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## Conversion of Alcohols into Amines by Borrowing Hydrogen

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# **Conversion of Alcohols into Amines by Borrowing Hydrogen**

**Malai Haniti Sheikh Abdul Hamid**

A thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry

University of Bath

November 2008

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And I dedicate this to my late father-in-law, Pg Ali Pg Hj Osman.

## **SYNOPSIS**

This thesis describes the development of a more economical catalytic system for the *N*-alkylation of amines by “borrowing hydrogen” and its application in the synthesis of a variety of amines including the dopamine agonist Piribedil and the antihistamine agents Antergan and Tripeleennamine.

**Chapter 2** describes the development of the ruthenium-catalysed *N*-alkylation of primary amines with primary alcohols by “borrowing hydrogen”.

**Chapter 3** describes the application of the ruthenium-catalysed *N*-alkylation of secondary amines with primary alcohols by “borrowing hydrogen”. The ruthenium-catalysed synthesis of dimethylamines by “borrowing hydrogen” is also described and a mechanistic proposal for the *N*-alkylation of alcohols with amines has been proposed.

**Chapter 4** describes the role of amines in pharmaceuticals and the ruthenium-catalysed synthesis of Piribedil, Antergan and Tripeleennamine by “borrowing hydrogen”.

## Abbreviations

Å	Angstrom
Abs.	Absolute
acac	Acetylacetone
anhyd.	Anhydrous
Ar	Aryl group
atm	Atmospheres
bmim	1-butyl-3-methylimidazolium
Bn	Benzyl
Bz	Benzoyl
b.p.	Boiling point
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>t</i> -butyloxycarbonyl
<i>c</i>	Concentration
COD	1,5-Cyclooctadiene
COT	1,3,5,7-Cyclooctatetraene
Cp*	Pentamethylcyclopentadienyl
crotyl	<i>trans</i> -but-2-en-1-yl
dba	Dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undecene-7
DEAD	Diethyl azodicarboxylate
dippf	1,1'-Bis(diisopropylphosphino)ferrocene
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DPEphos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppe	1,1'-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,1'-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray Ionisation
Et	Ethyl
Et <sub>3</sub> N	Triethylamine
EtOH	Ethanol

---

GLC	Gas-liquid chromatography
h	hours
HPLC	High pressure liquid chromatography
Hz	Hertz
<i>i</i>	<i>iso</i>
Im	Imidazole
<sup>i</sup> Pr	<i>iso</i> -propyl
<i>J</i>	Coupling constant
KO <sup>t</sup> Bu	Potassium <i>tert</i> -butoxide
LC	Liquid Chromatography
LiHMDS	Lithium hexamethyldisilazide
M	Molar
m.p.	Melting point
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
min	Minute
MPV	Meerwein-Ponndorf-Verley
MS	Molecular sieves
MW	Microwave
NaBH <sub>4</sub>	Sodium borohydride
NaCNBH <sub>4</sub>	Sodium cyanoborohydride
NMR	Nuclear Magnetic Resonance
<i>p</i>	<i>para</i>
PCy <sub>3</sub>	Tricyclohexyl phosphine
Ph	Phenyl
p <i>K</i> <sub>a</sub>	Acid dissociation constant
PPh <sub>3</sub>	Triphenyl phosphine
Pr	Propyl
<i>rac</i>	racemic
r.t.	Room temperature
RBF	Round-bottom Flask
R <sub>f</sub>	Retention factor
<i>t</i>	<i>tert</i>
<sup>t</sup> Bu	<i>tert</i> -Butyl



---

TEAF	Triethylammonium formate solution
Tf	Triflate
TFA	Trifluoroacetic acid
TfNHMe	<i>N</i> -methyltrifluoromethanesulfonamide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMOF	Trimethyl orthoformate
Triphos	1,1,1-tris(diphenylphosphinomethyl)ethane
TsDPEN	<i>N</i> -( <i>p</i> -toluenesulfonyl)-1,2-diphenylethylenediamine
UV	Ultraviolet
wt.	Weight
Xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthenes
$\delta$	Chemical shift

# Chapter 1

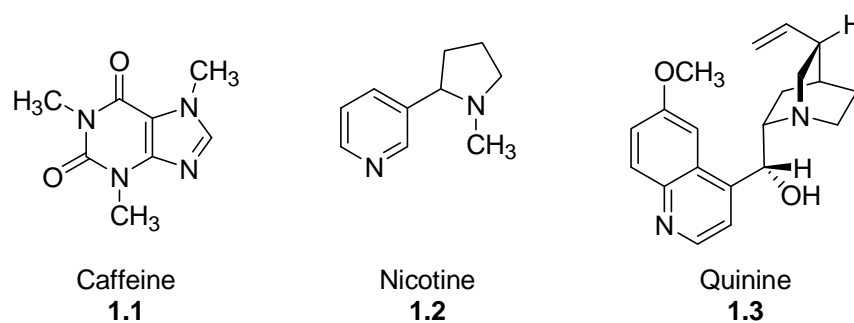
## 1. Introduction

Nitrogen is the fourth most common element in organic compounds. Although nitrogen is relatively inert; ammonia, the reduced form of nitrogen and its organic derivatives, the amines, are important in Nature.<sup>[1]</sup>

### 1.1 Amines

With a worldwide production of 100,000 t/a, this figure gives a rough picture of how important amines are.<sup>[2]</sup> Amines are an important class of compounds in bulk chemistry and also serve as important intermediates in organic synthesis. One example is ethylamine, which is the single most commercially important alkyl amine and accounts for about 35% to 40% of the world's annual requirement for alkyl amines.<sup>[3]</sup>

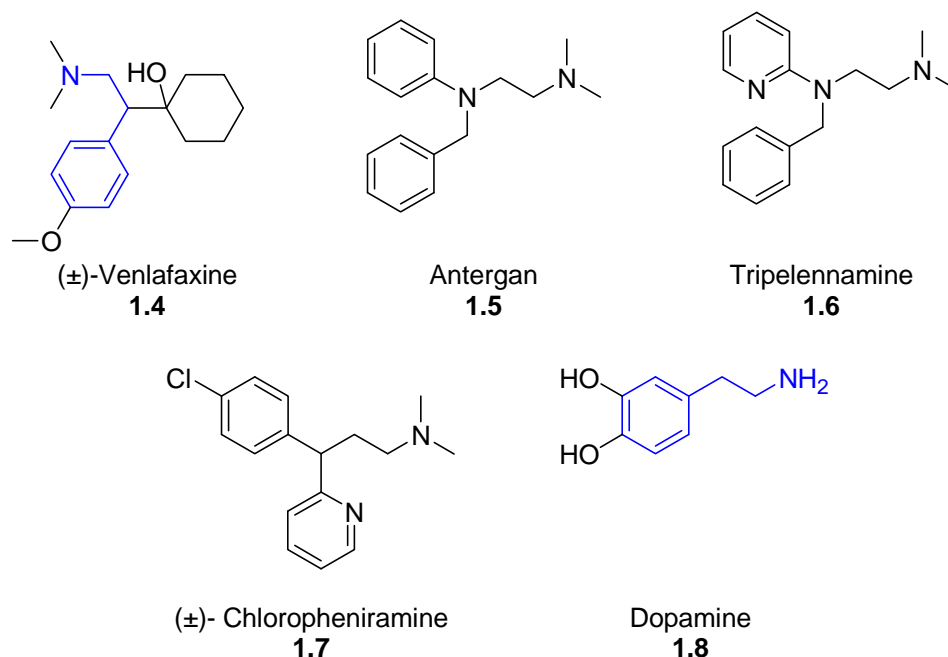
Basic amines derived from natural sources were traditionally known as “vegetable alkalis”, but they are now known as alkaloids.<sup>[4]</sup> Alkaloids vary from simple to enormously complex structures. Their basic nature gives rise to often potent physiological activity. Some representative alkaloids include caffeine **1.1**, nicotine **1.2** and quinine **1.3** shown in Figure 1.1.



**Figure 1.1** Structures of some representative alkaloids.

A large number of medicinally and biologically important compounds owe their activity to the presence of amino groups (Figure 1.2).<sup>[1]</sup> Many possess powerful physiological activity and others have been associated with a wide range of biological applications such as use as antidepressants, neurotransmitters and antihistamines. Venlafaxine (Effexor) **1.4** has an amino functional group and in 2007 was the 13<sup>th</sup> best selling prescription drug.<sup>[5]</sup> It is prescribed for the treatment of clinical depression and anxiety

disorders.<sup>[6]</sup> Antergan **1.5** was the first antihistamine to be used in man in 1942,<sup>[7]</sup> while Tripelennamine **1.6**, a classic antihistamine structurally similar to Antergan is still in use today to treat asthma, hay fever, rhinitis and urticaria.<sup>[8]</sup> Another prescribed drug is Chlorpheniramine (commonly marketed as Piriton) **1.7** commonly used to prevent symptoms of allergic conditions<sup>[9]</sup> and dopamine **1.8** is an important neurotransmitter in the brain. Abnormalities in the level of dopamine in the brain are associated with many psychiatric disorders such as Parkinson's disease.<sup>[4]</sup>



**Figure 1.2** Some medically important amines.

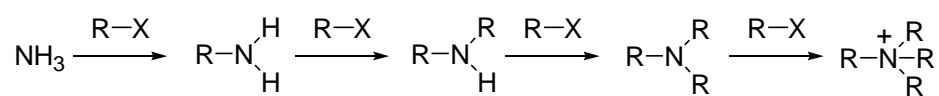
It is interesting to note that a common structural feature found in many medicinal drugs or biologically important compounds is the 2-phenylethanamine ( $\beta$ -phenethylamine) unit (Figure 1.2).<sup>[1]</sup> The structural similarities of these compounds could be related to their physiological and psychological effects. This unit appears to be crucial for the binding to brain receptor sites responsible for neurotransmitter action at certain nerve terminals that either control appetite and muscular activity or euphoric stimulation.<sup>[1]</sup> The application of amines in pharmaceuticals is discussed in further detail in Chapter 5.

Amines are also useful intermediates in the preparation of solvents, fine chemicals, cosmetics and azo dyes.<sup>[3]</sup> Another major application of amines is in the agrochemical industry. Some agrochemicals are pure amines, such as the herbicides based on pyridine, triazine or phenylene diamine, but an amide-based or urea-based agrochemical is often used which then gets metabolised to an amine.<sup>[3]</sup> Generally, amines and tertiary

amines, in particular, are one of the most common structural features of naturally occurring biologically active compounds as well as being important intermediates in the chemical industry.

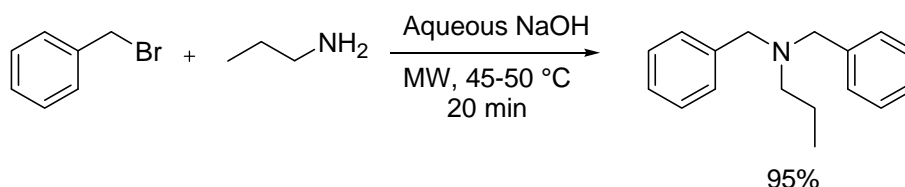
## 1.2 Synthesis of Amines

Amines are conventionally synthesised by the alkylation of alkyl halides<sup>[10]</sup> with ammonia or amines but over-alkylations are common leading to mixtures of primary, secondary, tertiary amines as well as quaternary ammonium salts (Scheme 1.1). This makes the purification process tedious and the method more expensive.



**Scheme 1.1** Overalkylation of amines.

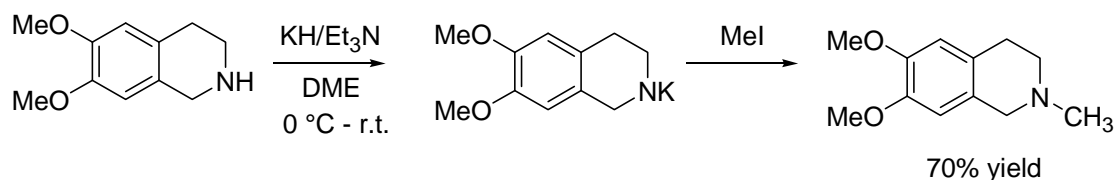
Use of a large excess of the starting amine could suppress overalkylation but this is an expensive and wasteful process.<sup>[11]</sup> One way to overcome this problem was reported by Varma *et al.* who developed a direct method for the generation of unfunctionalised tertiary amines *via* a microwave-assisted *N*-alkylation of primary or secondary amines by alkyl halides in aqueous media (Scheme 1.2).<sup>[12]</sup> By this method, tertiary amines including cyclic amines were synthesised with good to excellent yields. The same reaction depicted in Scheme 1.2 was performed under conventional heating and mixtures of products were formed in addition to side products such as benzyl alcohol (obtained as a result of hydrolysis of alkyl halides in alkaline medium). This method is atom-efficient, but requires the use of specialised microwave equipment and is not applicable to large scale preparation. The use of a strong inorganic base in stoichiometric amounts could again potentially harm base-sensitive functional groups.



**Scheme 1.2** Aqueous *N*-alkylation of a primary amine using microwave irradiation (MW power 250-300 W for 20 min).

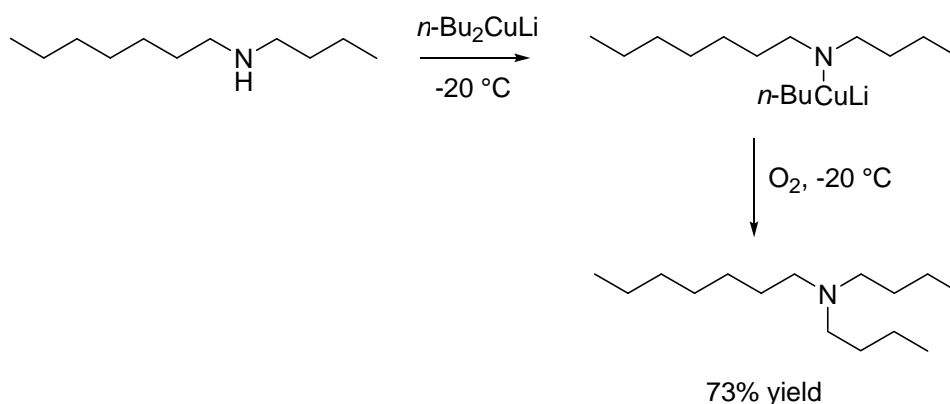
Another method reported by Mohri *et al.*<sup>[13]</sup> described a new modification of the selective *N*-alkylation reaction of secondary amines with alkyl halides in the presence of

excess potassium hydride and triethylamine (10 equiv.) to give the corresponding tertiary amines in satisfactory yields (Scheme 1.3). Triethylamine appeared to be a critical factor and it was presumed to act as a scavenger of excess alkyl halide. This is a useful method but the use of metal hydrides would present a problem particularly if either the secondary amine or alkyl halide contains acidic functional groups.



**Scheme 1.3** *N*-Alkylation of a secondary amine in the presence of triethylamine.

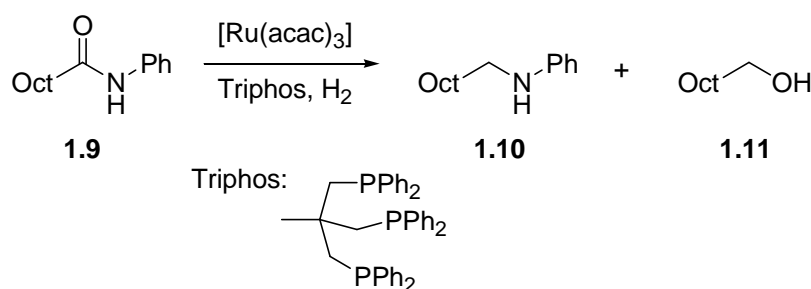
Organocopper reagents have also been used as alkylating reagents in the *N*-alkylation reactions of primary or secondary amines.<sup>[14]</sup> This approach is based on the oxidative coupling of a lithium alkylcopper amide that is formed *in situ* from lithium dialkylcuprates and the amine (Scheme 1.4). Excess amounts of the organocopper reagent and molecular oxygen are required for this transformation and only low to moderate yields are obtained.



**Scheme 1.4** *N*-Alkylation of amine with organocopper reagents.

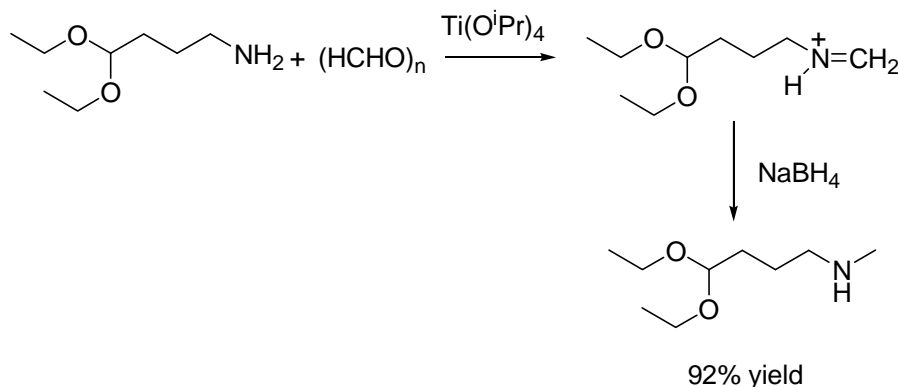
General synthetic methods for the preparation of amines have included amide reduction<sup>[15]</sup> or the well-known reductive amination of carbonyl compounds with primary and secondary amines. Hydrogenation of carboxylic acids and their derivatives is usually a difficult process because it requires harsh conditions, *e.g.* heterogeneous copper chromite at 250 °C and 300 bar of hydrogen.<sup>[16]</sup> Amides in particular give a mixture of primary, secondary and tertiary amines upon hydrogenation with copper chromite or Pd/Re/zeolite.<sup>[17]</sup>

There are only a few reports in the homogeneous hydrogenation of amides and one recent procedure has been reported by Cole-Hamilton and co-workers.<sup>[3]</sup> In the reported procedure, the hydrogenation of amides is carried out using a catalyst prepared *in situ* from  $[\text{Ru}(\text{acac})_3]$  and 1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos) (Scheme 1.5). When *N*-phenylnonamide **1.9** was used as substrate, in the absence of the ruthenium precatalyst, no conversion was obtained. A moderate yield of 61% was obtained when  $[\text{Ru}(\text{acac})_3]$  was used in the hydrogenation process while the combination of  $[\text{Ru}(\text{acac})_3]$  and triphos in the presence of water ( $\text{H}_2\text{O}:\text{solvent} = 1:9$ ) gave a full conversion and high selectivity to amine product **1.10** (93%). The alcohol **1.11** formed (7%) is thought to originate from the hydrolysis of amide to obtain the acid, or hydrolysis of imine to obtain the aldehyde followed by hydrogenation. It was found that water is required to stabilise the catalyst. The formation of primary amines using the same catalytic system in the hydrogenation of carboxylic acids in the presence of ammonia is also described.



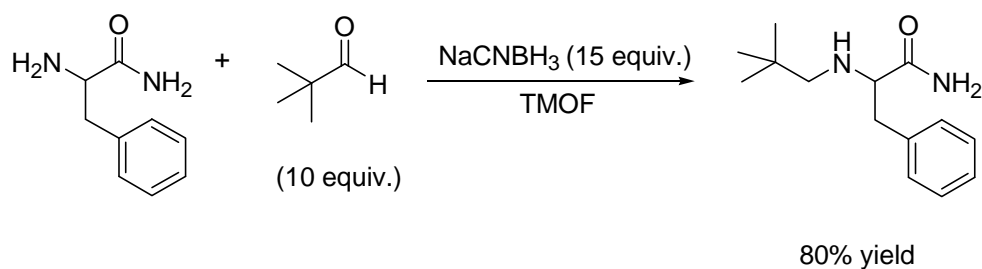
**Scheme 1.5** Hydrogenation of *N*-phenylnonamide catalysed by Ru/Triphos.

Reductive amination of carbonyl compounds with primary and secondary amines is an experimentally common procedure. Several reductants that have been used include sodium borohydride with titanium isopropoxide<sup>[18]</sup> and sodium cyanoborohydride.<sup>[19]</sup> The combination of sodium borohydride with titanium isopropoxide described by Bhattacharyya offers a mild and efficient one-pot reagent system in the reductive amination of formaldehyde with primary and secondary amines. The conditions were found to be tolerant to a number of acid-sensitive functional groups such as acetal, carboxylic ester, amide and carbamate (Scheme 1.6).<sup>[18]</sup>



**Scheme 1.6** Reductive amination with  $Ti(O^iPr)_4$  and  $NaBH_4$ .

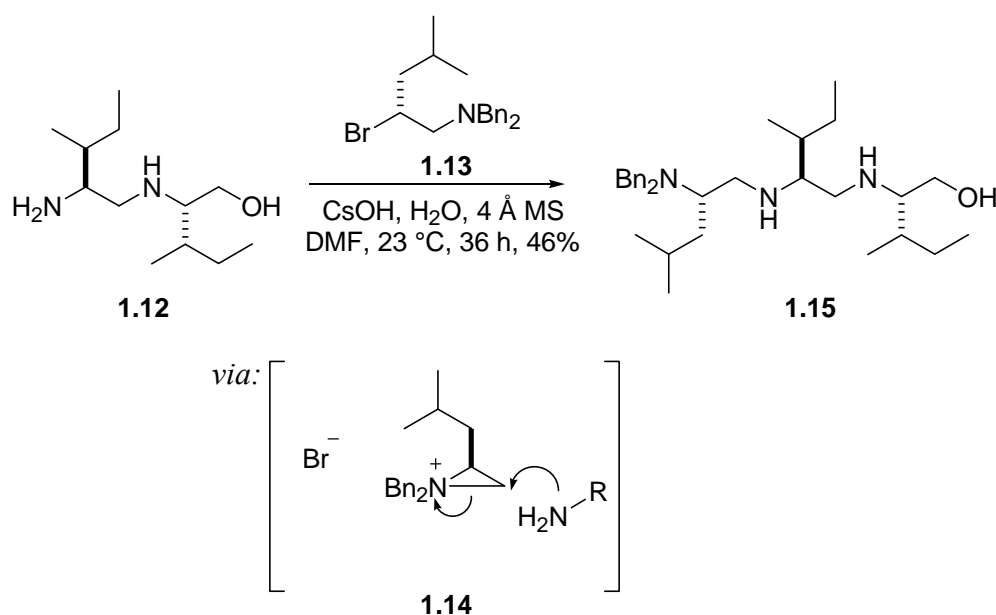
Reductive amination using sodium cyanoborohydride (Scheme 1.7) as reducing agent is widely used but it is expensive and the use of toxic sodium cyanoborohydride raises the risk of residual cyanide in the product or the work-up system. Although these different reductive amination methods give good yields, they require a large excess of the carbonyl compound and overalkylation is again often difficult to control.<sup>[20]</sup>



**Scheme 1.7** Reductive amination with  $NaCNBH_3$ .

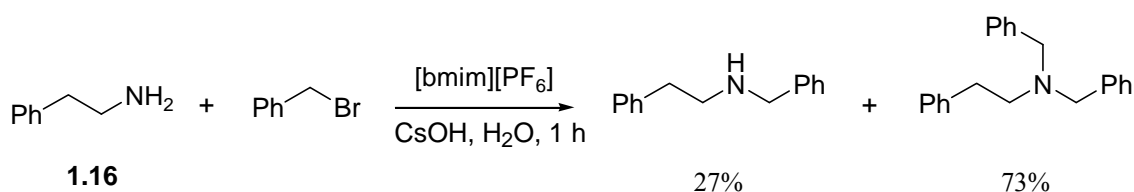
### 1.2.1 Synthesis of Secondary Amines

A comprehensive review by Salvatore *et al.*<sup>[21]</sup> described the synthesis of alkyl and aromatic secondary amines as well as some of their synthetic uses. The group has also developed the use of caesium bases in DMF in the mono-*N*-alkylation of primary amines, diamines and polyamines.<sup>[20]</sup> High chemoselectivities involved in amine and polyamine alkylations have been shown in this procedure. As shown in Scheme 1.8, the primary amine of dimer **1.12** reacted with protected amino bromide **1.13** selectively leaving both the secondary amine and the hydroxyl untouched. This afforded **1.15** cleanly, *via* an aziridinium intermediate **1.14**. Although this method is useful due to its mild reaction conditions and also labile functionalities are tolerated, it is limited to the syntheses of non-aromatic amines.



**Scheme 1.8** CsOH-promoted N-alkylation of dimer **1.12** with protected amino bromide **1.13** to afford trimer **1.15** cleanly via aziridinium intermediate **1.14**.

A simple method for the synthesis of secondary amines selectively using ionic liquids as solvent had recently been reported by Chiappe *et al.*<sup>[22]</sup> Secondary amines are formed by a nucleophilic substitution reaction between primary amines and alkyl tosylates or alkyl halides. Ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF<sub>6</sub>], have ultra-low volatility and therefore provide an advantage over volatile organic solvents. By this method, the reaction rate and the selectivity depend both on the nature of the reagents and on the type of leaving group, while the presence of caesium hydroxide and molecular sieves only affects the reaction rate. Whilst this method is simple and atom-efficient, over-alkylation is still a problem especially in reactions involving 2-phenylethylamine **1.16** as the starting amine (Scheme 1.9).

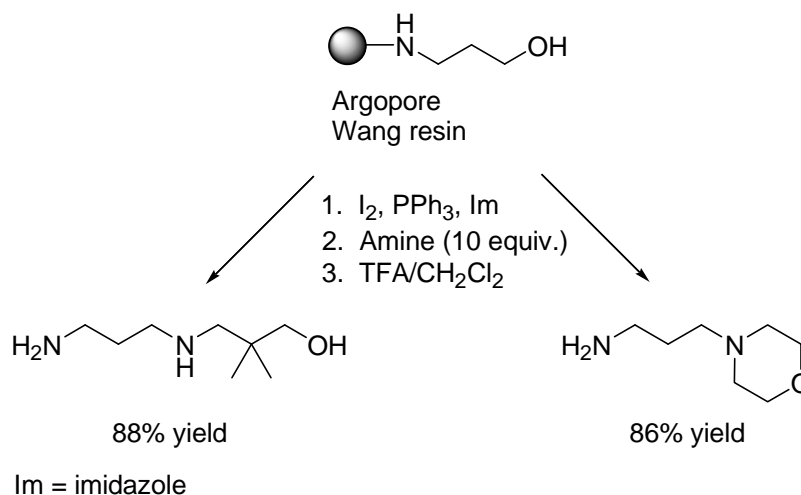


**Scheme 1.9** N-Alkylation of amine **1.16** with benzyl bromide in [bmim][PF<sub>6</sub>] to give mixtures of tertiary and secondary amine.

Solid-phase methods have demonstrated much potential for preparing targets more easily than classical methods. The formation of secondary and tertiary amino groups is an important step in the construction of polyamines on solid-phase supports and in the solid-phase synthesis of small organic molecules.<sup>[23]</sup> Olsen *et al.* for example,



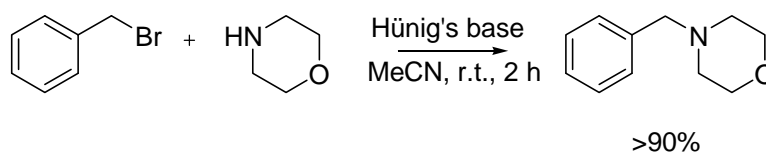
developed a solid-phase synthetic approach to secondary and tertiary amines that involves the conversion of resin-bound amino alcohols into the corresponding iodides, followed by iodide displacement with primary or secondary amines or with unprotected amino alcohols (Scheme 1.10).<sup>[24]</sup> Although this two-step procedure is considered useful for constructing libraries of secondary and tertiary amines, it is not practical for large-scale preparations because the process is considered a multistep procedure.



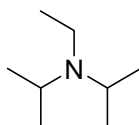
**Scheme 1.10** Solid-phase synthesis of amines via displacement of iodides on Argopore Wang resin.

### 1.2.2 Synthesis of Tertiary Amines

As mentioned earlier, one of the most frequently used procedures in the synthesis of tertiary amines is the *N*-alkylation of primary and secondary amines with alkyl halides in the presence of base. Hünig's base has been reported to be a suitable base for the direct formation of tertiary amines *via N*-alkylation of secondary amines by alkyl halides in acetonitrile (Scheme 1.11).<sup>[25]</sup> The reaction is favourable over other previously reported methods with respect to high product yields, scalability and operationally convenient conditions. However, the use of excess base (1.5 equiv.) in the reaction makes it unsuitable for base-sensitive functional groups and it is also undesirable from an environmental point of view.

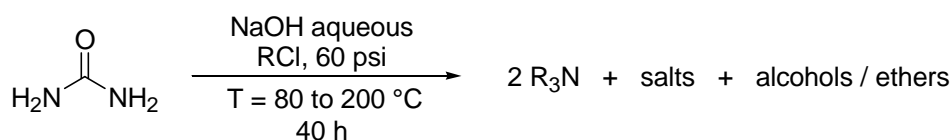


Hünig's base:



**Scheme 1.11** Direct alkylation of a secondary amine with an alkyl halide in the presence of Hünig's base.

Sachinvala *et al.* reported a one-step conversion of urea into tertiary amines. The synthesis was guided by the fact that in aqueous base such as NaOH, urea decomposes to ammonia, isocyanates and carbonate salts.<sup>[26]</sup> The sodium isocyanate could then alkylate to produce alkyl isocyanate which in turn can be converted into *N*-alkylcarbamic acid and then undergo decarboxylation. The resulting alkylamine could react further forming tertiary amines. It was postulated that in order to restrict the formation of tetrasubstituted ammonium salts, an excess of 3 molar equivalents of alkylating reagent and hydroxide base per nitrogen would be needed to keep the concentration negligible. Hence, a general method for making trisubstituted amines from urea was developed (Scheme 1.12). While this method is novel, a mixture of tertiary amine product, alcohols and ethers was obtained and a long reaction time of 40 hours is required to obtain good yields.

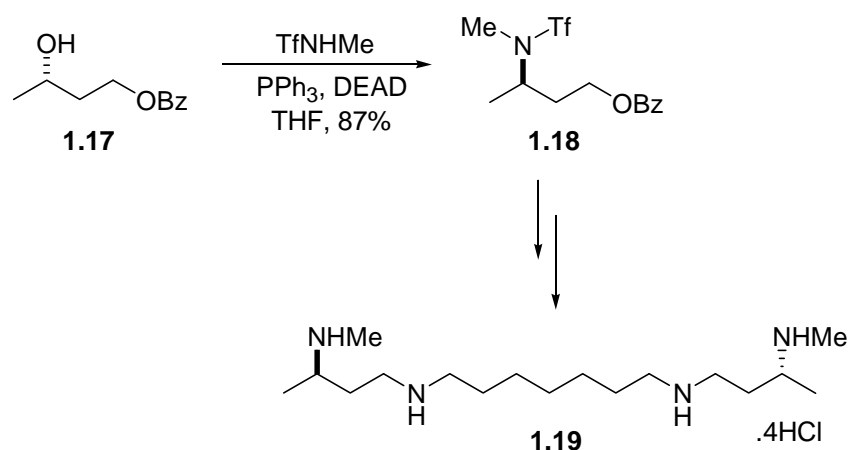


R = (% yield of isolated  $\text{R}_3\text{N}$ ):

allyl (56), crotyl (50), *n*-butyl (77), methallyl (72), *n*-octyl (75), benzyl (82)

**Scheme 1.12** Synthesis of trisubstituted amines from urea.

The Mitsunobu reaction employs a covalently activated amine derivative<sup>[21]</sup> used in the synthesis of amines. This reaction is a coupling of a primary or secondary alcohol with a compound containing an acidic proton (*e.g.* a sulfonamide) and is carried out in the presence of triphenylphosphine and diethylazodicarboxylate (DEAD). An example is depicted in Scheme 1.13.

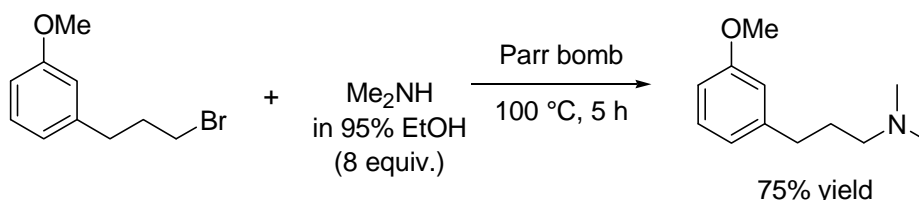


$\text{TfNHMe}$  = *N*-methyltrifluoromethanesulfonamide,  
(a sulfonamide)

**Scheme 1.13** Mitsunobu reaction between  $\text{TfNHMe}$  with benzoyl protected alcohol **1.17** to give triflate protected amine **1.18** which led to the synthesis of antitumour polyamine **1.19**.

This particular reaction (Scheme 1.13) led to the formation of an anti-tumour polyamine **1.19** after a series of synthetic steps.<sup>[28]</sup> Thereafter, more versatile Mitsunobu reagents have been developed.<sup>[29]</sup> However, in general, the Mitsunobu reaction is not often used on large scale due to the thermal hazards associated with azodicarboxylates.<sup>[30]</sup> One alternative method in the synthesis of amines is the use of solid phase supports.<sup>[31]</sup> They are useful in the construction of libraries of secondary and tertiary amines, but they are obviously not practical for large scale preparations.<sup>[25]</sup>

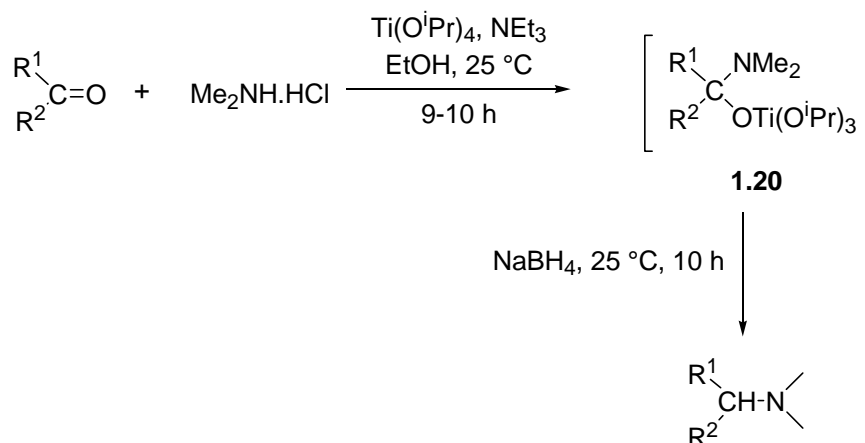
Tertiary amines containing dimethylamino functional groups are found in various important pharmaceuticals (see Figure 1.2 and Chapter 5) and are also useful as ligands in homogeneous catalytic asymmetric transformations.<sup>[32]</sup> The traditional approach to the synthesis of dimethylamines is the *N*-alkylation of dimethylamine with alkyl halides at high temperatures and pressure. An example is shown in Scheme 1.14 where a large excess of dimethylamine is required.<sup>[33]</sup>



**Scheme 1.14** *N*-Alkylation of  $\text{Me}_2\text{NH}$  with an alkyl halide.

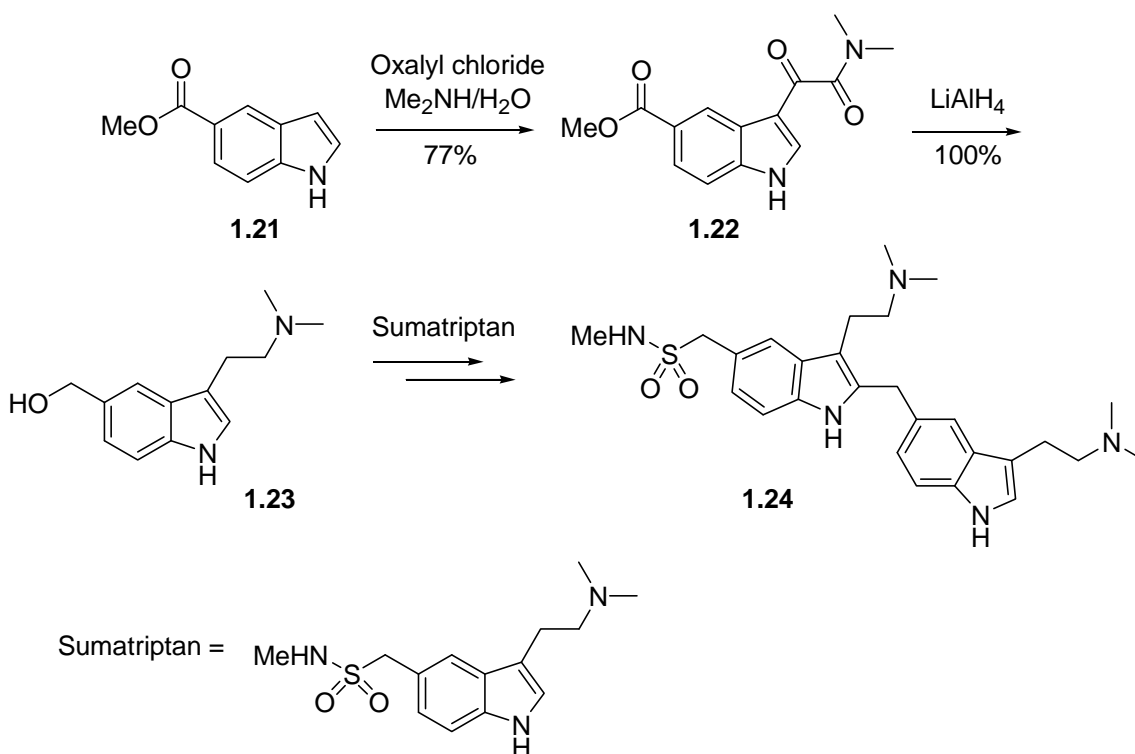
However, another direct approach is the reductive amination of aldehydes and ketones using the combination of titanium(IV) isopropoxide and sodium borohydride (previously described in Section 1.2). A mixture of dimethylamine hydrochloride and

triethylamine is used as the source of dimethylamine. The reaction is thought to proceed through the formation of titanium(IV) complex **1.20** (Scheme 1.15) as an intermediate which is reduced either directly or *via* a transient iminium species.<sup>[34]</sup> The reaction conditions are also compatible with reducible and acid-sensitive functional groups including acetonide, *tert*-butyldimethylsilyl ether and acetals. However, this system needs titanium(IV) isopropoxide as a Lewis acid and requires long reaction times.



**Scheme 1.15** Reductive alkylation of dimethylamine using titanium(IV) isopropoxide and  $\text{NaBH}_4$ .

Another dimethylation procedure described in the literature is a two-step procedure used in the synthesis of compound **1.24**, the main Sumatriptan impurity (Scheme 1.16).<sup>[35]</sup> The procedure involves the acylation of compound **1.21** in the 3-position with oxalyl chloride and dimethylamine to give intermediate **1.22**. This is followed by reduction of the amide, ketone and ester groups simultaneously to give the dimethyamino compound **1.23** with  $\text{LiAlH}_4$ .

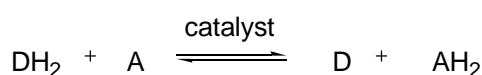


**Scheme 1.16** Synthesis of main Sumatriptan impurity **1.24**.

There are various other methods of synthesising amines that include: electrophilic or nucleophilic addition to alkenes,<sup>[36]</sup> Staudinger reaction,<sup>[37]</sup> Buchwald-Hartwig amination,<sup>[38]</sup> hydroaminomethylation,<sup>[39]</sup> hydroamination<sup>[40]</sup> and *N*-alkylation of alcohols. However, the direct *N*-alkylation of amines with alcohols is a more atom-efficient and environmentally friendly method in the synthesis of amines since this transformation produces water as the only by-product.<sup>[41]</sup> This will be discussed in further detail in Section 1.4.

### 1.3 Transition Metal-Catalysed Transfer Hydrogenation

Hydrogen-transfer or transfer hydrogenation is defined as the reduction of multiple bonds by a hydrogen donor in the presence of a catalyst.<sup>[42]</sup> The process undergoes abstraction of hydrogen from an organic molecule as the hydrogen donor *via* a catalyst, followed by hydrogen addition to the unsaturated functional group of the hydrogen acceptor (Scheme 1.17).<sup>[42b]</sup>



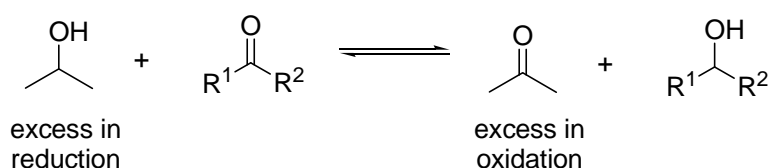
DH<sub>2</sub> = hydrogen donor; A = hydrogen acceptor

**Scheme 1.17** Transfer hydrogenation equation.

In comparison with conventional catalytic reduction using molecular hydrogen, transfer hydrogenation is preferred because it excludes the use of hazardous molecular hydrogen that require gas containment and pressure vessels, while the use of hydrogen donors only requires simple stirring of solutions.<sup>[43]</sup> There are several substrates that make suitable hydrogen acceptors (H-acceptors) and these include ketones,  $\alpha,\beta$ -unsaturated carbonyl compounds,  $\alpha,\beta$ -unsaturated acids and esters, and imines and nitro compounds.<sup>[42b]</sup>

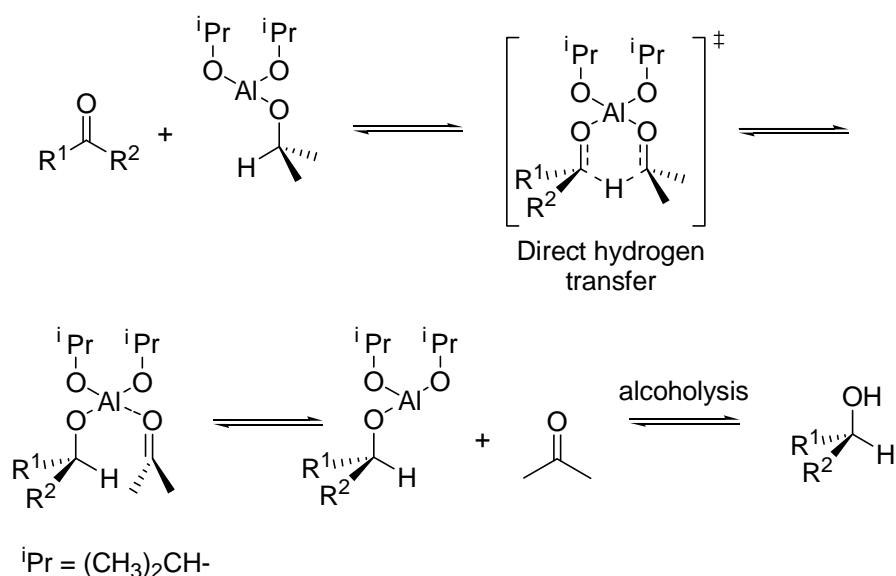
The discovery of transfer hydrogenation dates back to 1903 when Knoevenagel first reported that dimethyl 1,4-dihydroterephthalate disproportionated readily in the presence of palladium black to dimethyl terephthalate and (mostly *cis*) hexahydroterephthalate<sup>[44]</sup> and then, since 1925, the Meerwein-Ponndorf-Verley (MPV) reduction was introduced when Meerwein and Schmidt reduced an aldehyde with ethanol in the presence of aluminium ethoxide.<sup>[45]</sup> During the same year, the reduction of butyraldehyde using aluminium ethoxide and aluminium isopropoxide was reported by Verley<sup>[46]</sup> and then followed by Ponndorf who showed that aldehydes and ketones can be easily reduced by oxidisable secondary alcohols in the presence of aluminium isopropoxide.<sup>[47]</sup> The reaction was referred to as the Meerwein-Ponndorf-Verley reduction (MPV).

The reaction can be carried out in the opposite direction as reported by Oppenauer in 1937 whereby the oxidation of steroids containing secondary alcohol moieties can be obtained in high yield using acetone in benzene as the oxidant and aluminium *tert*-butoxide as catalyst.<sup>[48]</sup> Hence, by comparison, the Oppenauer oxidation uses acetone in excess while the MPV reduction of ketone (transfer hydrogenation) uses isopropanol in excess. The Oppenauer oxidation is effectively an MPV reduction in reverse and the reaction type is frequently referred to as MPV-O or Meerwein-Ponndorf-Verley-Oppenauer (Scheme 1.18). Several reviews on the MPVO reactions have been published.<sup>[49]</sup>



**Scheme 1.18** *MPV reduction and Oppenauer oxidation.*

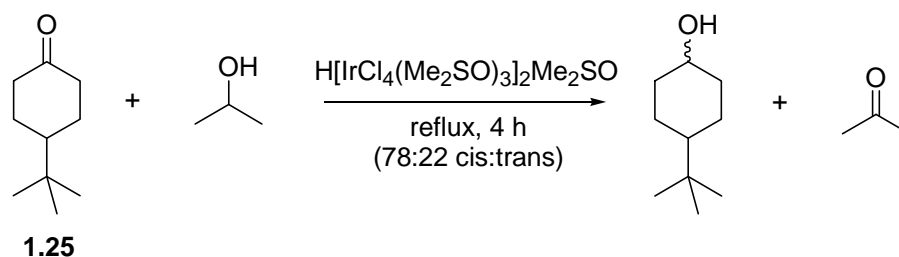
The generally accepted mechanism of the MPV-O is through a “direct hydrogen transfer” depicted in Scheme 1.19 that proceeds through a six-membered cyclic transition state without the involvement of a metal hydride species. The alcohol is coordinated as the alkoxide. Upon coordination to Al(III), the carbonyl is activated to nucleophilic attack and therefore initiates the hydride shift from the alkoxide to the carbonyl group *via* a six-membered transition state. The alkoxide product is released from the transition state after abstraction of a proton upon work-up. Among the important features of the reaction is that it is completely reversible and the removal of the ketone or the addition of excess isopropyl alcohol shifts the equilibrium to the right, aldehydes react faster than ketones and the method is sensitive to steric hindrance, so sterically hindered aldehydes and ketones are reduced more slowly than unhindered ones.<sup>[50]</sup> However, one of the limitations of the MPV-O system is that stoichiometric amounts (one or more equivalents for ketones) of the aluminium alkoxides are often used. Some side reactions do occur as well such as the aldol condensation of aldehyde substrates and the Tishchenko reaction of aldehyde substrates with no  $\alpha$ -hydrogen atom, but this can be controlled by the use of anhydrous solvents.



**Scheme 1.19** Mechanism of MPV-O reaction using  $\text{Al}(\text{O}^i\text{Pr})_3$ .

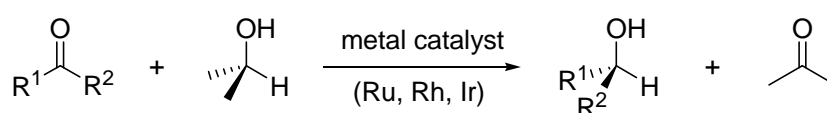
It was in 1952 that Braude and Linstead described the remarkable discovery that ethylenic and acetylenic linkages can be reduced by refluxing with cyclohexene in tetrahydrofuran in the presence of palladium black in high yield.<sup>[51]</sup> Subsequent studies also showed aliphatic and aromatic nitro groups as well as azo, azoxy and azomethine groups undergo reduction under the same conditions. However, carbonyl groups were resistant to reduction except when part of a potential aromatic system such as quinones

or decalones. Henbest in the 1960s reported the first example of a transition metal-catalysed hydrogen transfer using an iridium hydride DMSO complex as a catalyst.<sup>[52]</sup> This process showed that a hydride,  $\text{H}[\text{IrCl}_2(\text{Me}_2\text{SO})_3]$  was produced when a solution of the acid,  $\text{H}[\text{IrCl}_4(\text{Me}_2\text{SO})_3]_2\text{Me}_2\text{SO}$  in isopropanol was refluxed for 4 hours and catalysed the reduction of 4-*tert*-butylcyclohexanone **1.25** (Scheme 1.20). Acetone was formed in the reaction and it is similar to MPV reduction but only smaller amounts of soluble catalyst are required for the reaction.



**Scheme 1.20** First example of a transition metal-catalysed hydrogen transfer using iridium hydride-DMSO complexes.

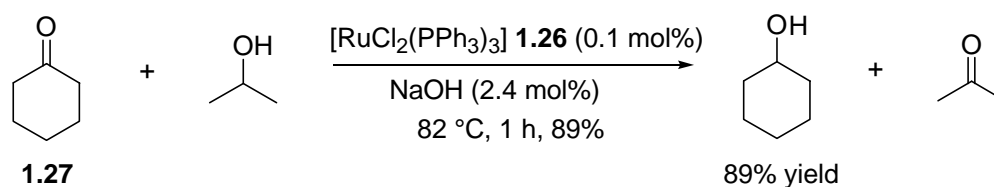
Later, in the 1970s, Sasson and Blum reported the first ruthenium-catalysed hydrogen transfer reaction. However, by this method, the first generation catalyst such as  $[\text{RuCl}_2(\text{PPh}_3)_3]$  **1.26** only showed low catalytic activity and also required high reaction temperature.<sup>[53]</sup> It is only in the last two decades that major advances in the catalytic hydrogen transfer reaction have been accomplished (Scheme 1.21).<sup>[54]</sup> This includes the discovery of more active catalysts and more efficient hydrogen donors which are able to undergo high reaction rates under mild conditions.<sup>[42b]</sup>



**Scheme 1.21** Catalytic hydrogen transfer processes.

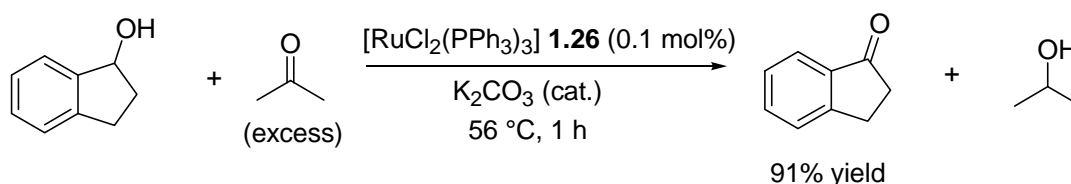
In 1991, Bäckvall *et al.* reported the effect of base on the  $[\text{RuCl}_2(\text{PPh}_3)_3]$ -catalysed transfer hydrogenation.<sup>[55]</sup> The addition of small amounts of base was found to increase the catalyst activity dramatically. For example, a full conversion was obtained within 1 hour when 0.1 mol% of  $[\text{RuCl}_2(\text{PPh}_3)_3]$  **1.26** was used in the presence of 2.4 mol% of NaOH in the transfer hydrogenation of cyclohexanone **1.27** (Scheme 1.22).





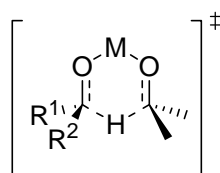
**Scheme 1.22** Effect of base in  $[\text{RuCl}_2(\text{PPh}_3)_3]$ -catalysed transfer hydrogenation.

Without the addition of base to the system, transfer hydrogenation did not occur. It was later shown that the increase in reactivity is due to the formation of a highly active dihydride species,  $[\text{RuH}_2(\text{PPh}_3)_3]$ .<sup>[55b]</sup> Also, an enhancement in the reaction rate was observed due to the effect of base for the reversed reaction (the Oppenauer-type oxidation) (Scheme 1.23).<sup>[56]</sup> This was an important breakthrough, as these reactions proceed under mild conditions with low catalyst loading and previously ruthenium-catalysed transfer hydrogenation systems had always required high temperatures.<sup>[53b]</sup>



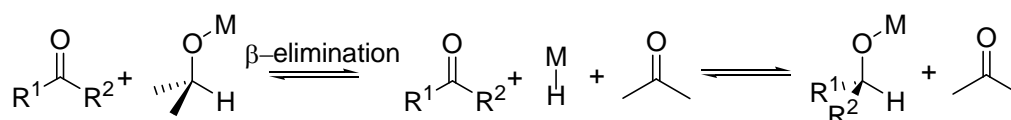
**Scheme 1.23** Effect of base in the transfer dehydrogenation of alcohols by **1.26**.

There are two discrete reaction mechanisms that have been described for the transfer hydrogenation of ketones<sup>[42b]</sup> and several reviews describing these mechanisms have been published.<sup>[57]</sup> Firstly, is the “direct hydrogen transfer” similar to the Meerwein-Ponndorf-Verley (MPV) reduction process described earlier. It is a concerted process that involves a six-membered cyclic transition state. The hydrogen donor ( $i\text{PrOH}$ ) and the hydrogen acceptor (ketone) are in close proximity to the metal centre (Figure 1.3). This pathway is thought to occur with non-transition metals.<sup>[55b]</sup>



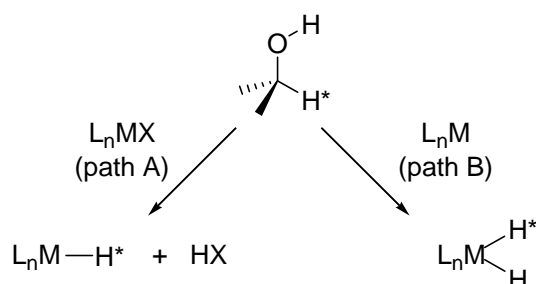
**Figure 1.3** Six-membered cyclic transition state in the “direct hydrogen transfer” mechanism for non-transition metals.

Secondly, is the “hydridic route”. In this pathway, a metal hydride is involved in the hydrogen transfer (Scheme 1.24). Transition metal complexes, as stated by Noyori, “prefer the hydride mechanism”.<sup>[57c], [58]</sup>



**Scheme 1.24** Reaction mechanism for the “hydridic route”.

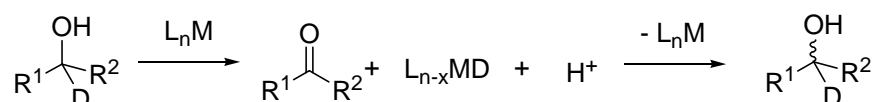
Additionally, there are two different pathways for the hydridic route depending on the origin of the hydride on the metal (Scheme 1.25).



**Scheme 1.25** Two different pathways proposed for the hydridic route.

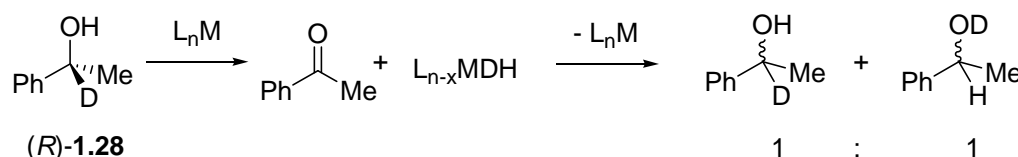
Path A is called the *metal monohydride* mechanism resulting in selective carbon-to-carbon hydrogen transfer and Path B is the *metal dihydride* mechanism resulting in nonselective hydrogen transfer involving both oxygen-to-carbon and carbon-to-carbon hydrogen transfer. By deuterium labelling of the donor alcohol and the use of the corresponding ketone as the hydrogen acceptor, Bäckvall *et al.* have described the racemisation of an enantiomerically pure  $\alpha$ -deuterated alcohol in order to distinguish between the two.<sup>[59-60]</sup>

For the metal monohydride mechanism, a common feature for the catalysts is that the hydride and the proton keep their identity, *i.e.* the C-H from the hydrogen donor ends up as a C-H in the product. This means that the C-H hydrogen of the donor forms the hydride on the metal (that transfers to the carbonyl carbon) while the OH of the donor stays as a proton during the process and adds to the carbonyl carbon. Hence, the deuterium will only end up in the  $\alpha$ -position of the fully racemised alcohol (Scheme 1.26).



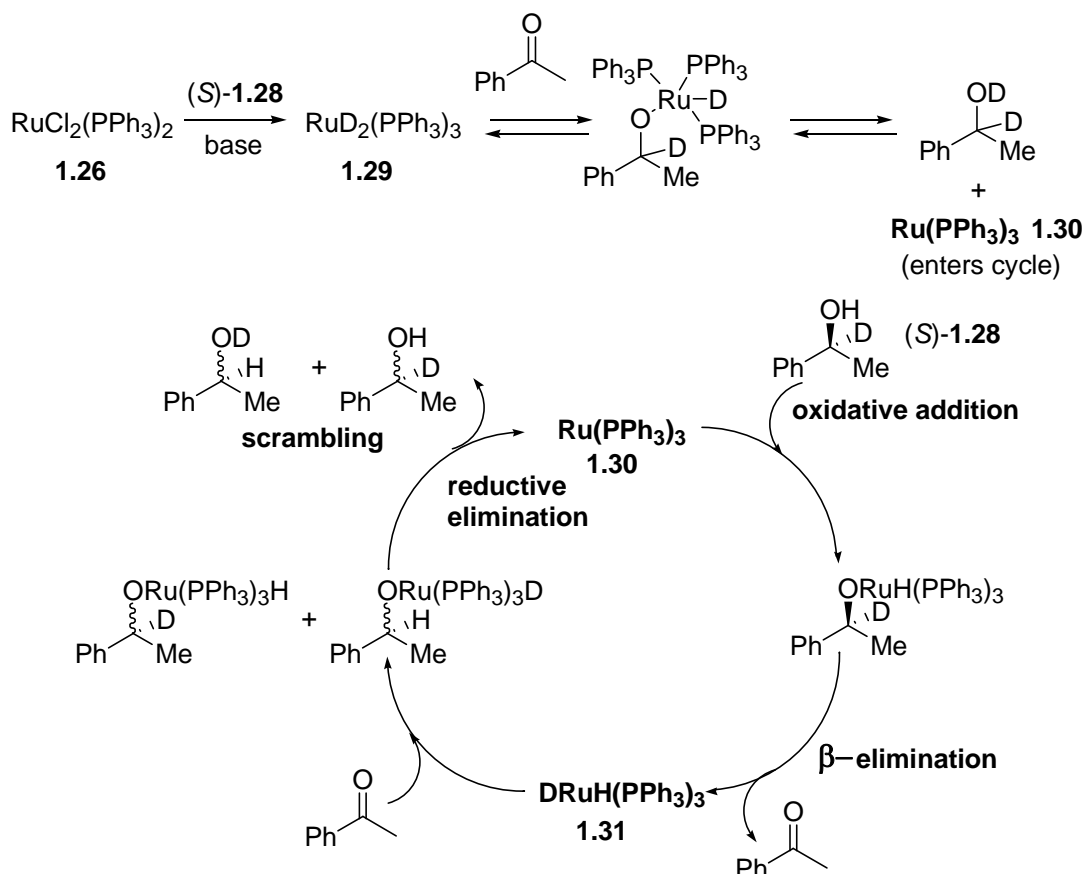
**Scheme 1.26** Racemisation of  $\alpha$ -deuterated chiral alcohol in the monohydride mechanism.

For the dihydride mechanism, a general feature for the catalysts is that the C-H and O-H from the hydrogen donor (alcohol or formic acid) lose their identity when they are transferred to the ketone (or aldehyde). This is because the two hydrogens become equivalent after being transferred to the metal to give the dihydride. Racemisation studies on (*R*)-phenylethanol **1.28** show that if the catalysts follow the dihydride mechanism, the deuterium will be scrambled between carbon and oxygen (C-D:O-D ~ 1:1) (Scheme 1.27).



**Scheme 1.27** Racemisation of  $\alpha$ -deuterated (*R*)-**1.28** in the dihydride mechanism.

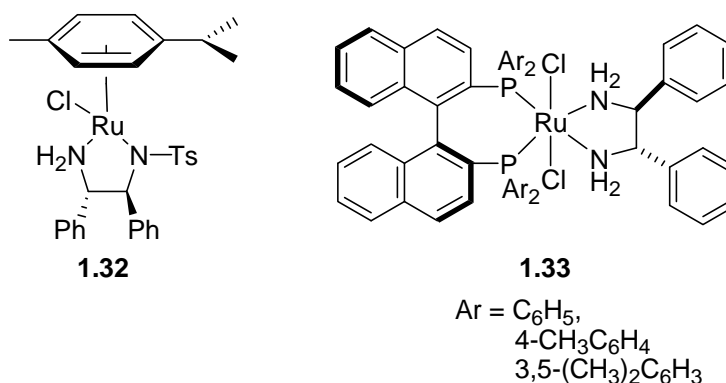
From these mechanistic studies, Bäckvall *et al.*<sup>[59], [60]</sup> indicated that iridium and rhodium-catalysed hydrogen transfer were found to follow the monohydride mechanism, while ruthenium-catalysed hydrogen transfer could follow either the dihydride or monohydride pathway depending on the ligands. The mechanism for the metal dihydride pathway for  $[\text{RuCl}_2(\text{PPh}_3)_3]$  **1.26** as catalyst has been proposed and is shown in Scheme 1.28.



**Scheme 1.28** Proposed catalytic cycle of transfer hydrogenation via a metal hydride.

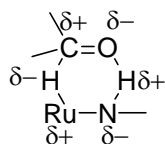
This mechanism involves the formation of a ruthenium dideuteride **1.29** from the reaction of **1.26** with the alcohol in the presence of base. The ruthenium dideuteride in turn reacts with the ketone to give an alkoxyruthenium complex, which gives a highly reactive Ru(0) species **1.30** after reductive elimination. This ruthenium species enters the cycle and oxidative addition of (*S*)-**1.28** to **1.30** gives an alkoxide complex. A mixed hydride-deuteride **1.31** is then formed after a  $\beta$ -hydride elimination from the alkoxide complex. Finally, the addition of **1.31** to acetophenone and subsequent reductive elimination gives the scrambled alcohols. This shows that a ruthenium dihydride is the intermediate in the  $\text{RuCl}_2(\text{PPh}_3)_3$ -catalysed hydrogen transfer.

The most notable transfer hydrogenation system was reported by Noyori *et al.* in 1995. It incorporates the Ru(II)-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst in the asymmetric transfer hydrogenation of ketones, whereby good to excellent ee's were obtained with 2-propanol as hydrogen donor and as solvent.<sup>[61]</sup> Noyori has coined the term “metal ligand bifunctional catalyst” for his catalysts such as **1.32** and **1.33**.



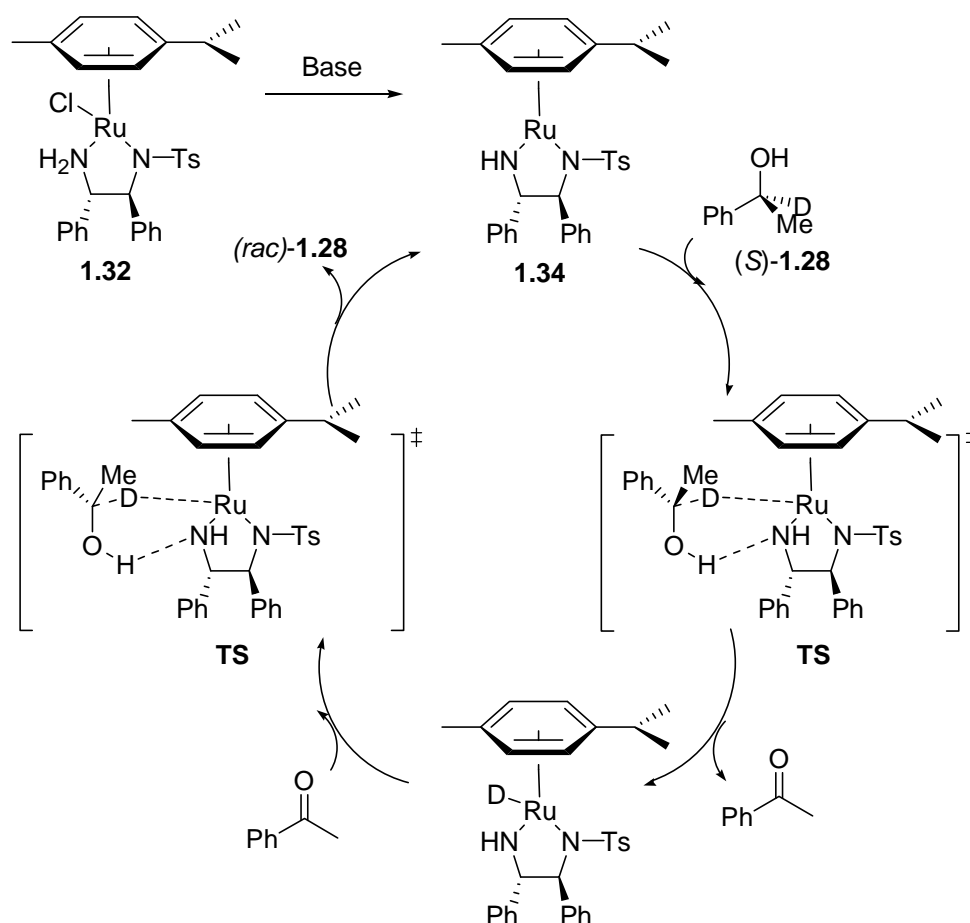
**Figure 1.4** Noyori's catalysts.

The nonclassical metal-ligand bifunctional mechanism of these catalysts involves a metal hydride intermediate.<sup>[62]</sup> Hydride transfer from the metal to the carbonyl carbon involves a six-membered pericyclic transition state whereby a Ru hydride species possessing an NH<sub>2</sub> ligand, whose hydridic Ru-H and protic N-H are simultaneously transferred to the C=O linkage. This forms an alcoholic product directly, without forming a metal alkoxide (Figure 1.5). The metal and the ligand participate cooperatively in the bond-forming and bond-breaking processes in this type of hydrogenation.



**Figure 1.5** Nonclassical metal-ligand bifunctional mechanism.

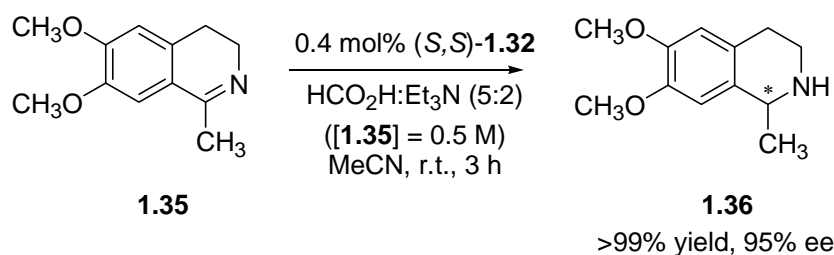
A more detailed mechanism is depicted in Scheme 1.29. Note that the reaction is proposed to proceed without coordination of either alcohol or ketone (aldehyde) to the metal. An important feature of these complexes is that the addition of external base is not required as a co-catalyst, since one of the coordinating sites of the ligand acts as a basic centre.<sup>[59]</sup> This mechanism has received considerable attention in recent years and has been subjected to extensive theoretical and kinetic studies.<sup>[63]</sup>



**Scheme 1.29** Proposed concerted proton and hydride transfer mechanism for the racemisation of (*S*)-**1.28** with catalyst **1.32**.

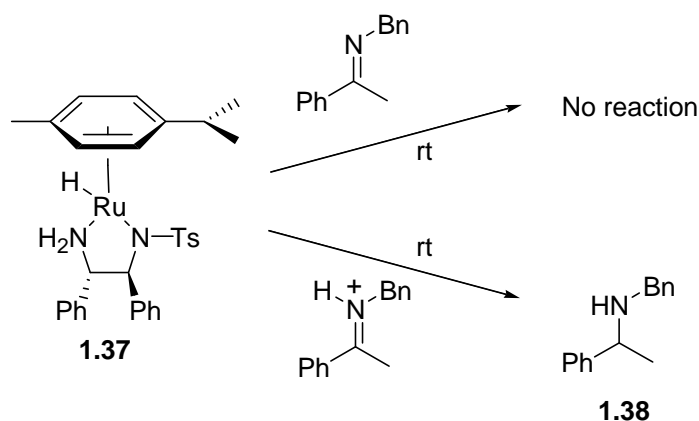
Reduction of C=N bonds is of great interest since as described before amines are present in many medicinal drugs (Chapter 1.1). Generally, nitrogen containing functional groups are preferentially reduced with an azeotropic 5:2 mixture of HCOOH and NEt<sub>3</sub> (TEAF) rather than with isopropanol as hydrogen donor.<sup>[57a]</sup> Noyori has used this azeotrope to reduce imines with high ee's using the ruthenium catalyst Ru(II)-

TsDPEN **1.32** under mild conditions.<sup>[64]</sup> For example, the asymmetric reduction of **1.35** was best carried out with TEAF in acetonitrile containing (*S,S*)-**1.32** at 28 °C leading to (*R*)-**1.36** in 95% ee and in >99% yield (Scheme 1.30).



**Scheme 1.30** Asymmetric hydrogenation of imine with Noyori's catalyst (*S,S*)-**1.32**.

The reduction using a rhodium-based complex, such as  $[\text{Cp}^*\text{RhCl}_2]_2$  with the mono-*N*-tosylated diamine (*S,S*)- $\text{TsNHCH}_2\text{CH}_2\text{NH}_2$  as ligand, proceeds at a considerably higher rate than those using Ru-based catalysts.<sup>[65]</sup> However, the latter ones provide consistently higher ee's. The reactivity order for catalyst **1.37** is linked with the polarisation of the double bond of the substrates which explains why aldehydes react faster than ketones (Scheme 1.31). Imines have a less polarised double bond and therefore require harsher reaction conditions than aldehydes and ketones. As described before, aldehydes and ketones are easily reduced in isopropanol, whereas imines require a TEAF mixture.<sup>[64]</sup> Bäckvall *et al.* recently established that imines are not reduced by the complex **1.37** which indicates that imines must follow a different reaction pathway to that proposed for ketones and aldehydes.<sup>[66]</sup> However, in the presence of acid the imine reacts with hydride **1.37** to give amine **1.38**. This is presumably due to the protonation of the imine by the acid and therefore activating it prior to hydride transfer (Scheme 1.31).



**Scheme 1.31** Imines do not follow the same reaction pathway as carbonyls in the hydrogenation by complex **1.32**.

The discovery of these catalysts has led to the development of a number of catalytic systems such as metal-based bifunctional catalytic systems that are effective for C-H, C-C, C-O or C-N bond formation,<sup>[67]</sup> water-soluble catalytic systems,<sup>[68]</sup> use of *N*-heterocyclic carbenes as alternative ligand environment for organometallic catalysis<sup>[69]</sup> as well as new catalytic systems under base-free conditions.<sup>[70]</sup> Developments in homogeneous organometallic catalysis will steadily gain momentum due to its direct application in various industries.<sup>[71]</sup>

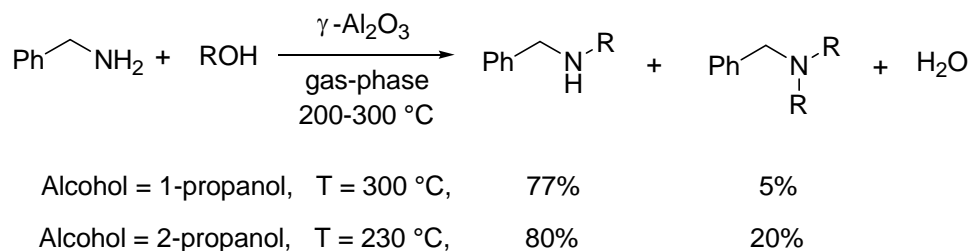
## 1.4 *N*-Alkylation of Amines with Alcohols

The *N*-alkylation of amines with alcohols is a method for forming a carbon-nitrogen bond which involves the direct condensation between an amine and an alcohol. It is an attractive and promising alternative to traditional alkylating procedures due to several factors: (i) it is a safer and non-toxic procedure, (ii) water is generated as a by-product and avoids production of wasteful products, (iii) alcohols are inexpensive and more readily available than the corresponding toxic halides or carbonyl compounds and the selectivity of the reaction can be controlled with the catalyst.<sup>[72-73]</sup> At present, there is still a heavy reliance on the use of alkylating agents especially for carbon-nitrogen bond formation in the design of syntheses as pointed out in a recent review on reactions in the pharmaceutical industry.<sup>[30]</sup> Stringent requirements that only minute levels of residual genotoxic impurities are permitted in drug candidates is a problem and the need for methods to alkylate amines with alcohols was highlighted in the review.

The direct alkylation of amines with alcohols has been known since the beginning of the 20<sup>th</sup> century when Sabatier first reported the first *N*-alkylation of amines with alcohols over ThO<sub>2</sub> catalyst.<sup>[74]</sup> However, the reaction conditions were difficult for industrial application.<sup>[75]</sup> Since then, this method had been extensively explored using different additives such as acids like H<sub>2</sub>SO<sub>4</sub>,<sup>[76]</sup> use of zeolites,<sup>[77]</sup> silica supported vanadia catalysts<sup>[78]</sup> or  $\gamma$ -alumina<sup>[79]</sup> in a fixed-bed integral-flow reactor at atmospheric pressure.

As shown in Scheme 1.32, Valot *et al.*<sup>[75]</sup> reported a selective method for the *N*-alkylation of amines (aromatic or aliphatic, mono- or di-alkylation) with a variety of alcohols using cheap  $\gamma$ -alumina as a catalyst at atmospheric pressure and high selectivity in favour of the monoalkylated product was found. Additionally, the reaction conditions were also performed with enantiomerically pure  $\alpha$ -methylbenzylamine and GC analysis showed no racemisation occurred during the reaction and thus it is

compatible with chirality. Although this method is solvent free and utilises cheap alumina, high temperature conditions are required that may prove to be unsuitable to temperature labile substrates.



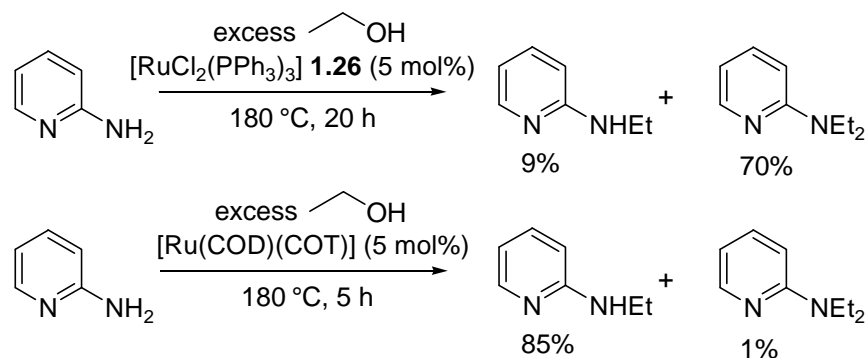
**Scheme 1.32** Gas-phase selective *N*-alkylation of amines with alcohols over alumina.

Transition metal catalysts have been known to catalyse the *N*-alkylation reaction of amines and alcohols, including the use of nickel as a heterogeneous catalyst for this reaction.<sup>[80]</sup> Until now *N*-alkylation of amines with alcohols are performed at high pressure and temperatures >200 °C.<sup>[81]</sup>

The first homogeneous catalysts in the amination of alcohols were introduced by Grigg *et al.*<sup>[82]</sup> and Watanabe *et al.*<sup>[83]</sup> in 1981. Subsequently, catalytic systems using ruthenium,<sup>[41], [84-85]</sup> rhodium,<sup>[86]</sup> platinum,<sup>[87]</sup> and iridium<sup>[86], [88]</sup> complexes have been reported. We have recently published a review on the amination of alcohols *via* homogeneous catalysis in particular as well as applications to the synthesis of C-C bonds from alcohols using a related strategy and highlights from the review (several procedures) shall be described.<sup>[89]</sup>

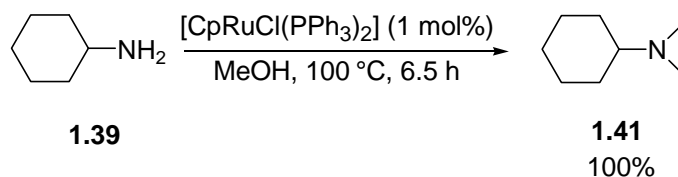
The disadvantages of the known homogeneous catalysts similarly to heterogeneous systems, are the high temperatures and long reaction times which are usually required to obtain optimum yields. For example, in 1996 Watanabe *et al.* reported the first example of *N*-alkylation of heteroatomic amines with alcohols. By this method, *N*-monoalkylation and *N,N*-dialkylation of aminopyridines can be controlled by the use of catalysts [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] **1.26** and [Ru(COD)(COT)] (Scheme 1.33).<sup>[84]</sup>





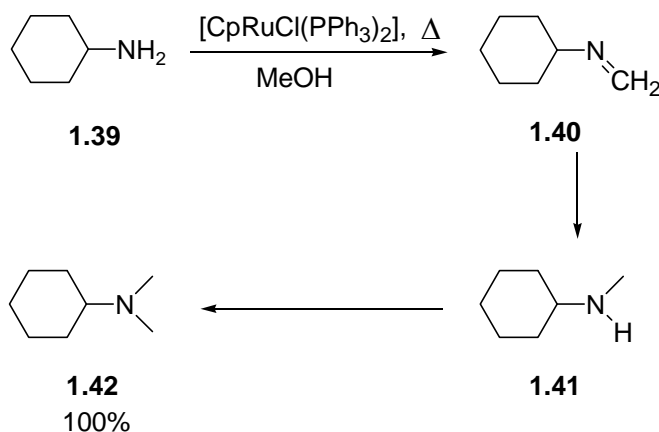
**Scheme 1.33** *N*-Alkylation of heteroatomic amines with alcohols using ruthenium catalysts.

Recently, several iridium and ruthenium catalysts were shown to be effective for the amination of alcohols at moderate temperatures (80–110 °C). Del Zotto<sup>[41]</sup> *et al.* reported the *N*-methylation of amines with methanol using a ruthenium(II) half-sandwich complex  $[\text{CpRuCl}(\text{PPh}_3)_2]$  (Scheme 1.34). This method is quite efficient as it provides fast and quantitative conversion and requires non-forcing conditions since the reaction is carried out in methanol at reflux.



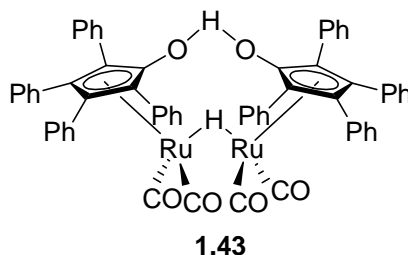
**Scheme 1.34** *N*-Methylation of alkylamines with  $[\text{CpRuCl}(\text{PPh}_3)_2]$ .

The reaction between methanol and cyclohexylamine **1.39** was monitored by GC-MS in order to study the *N*-methylation process in detail. It was found that the reaction proceeds stepwise (Scheme 1.35), whereby the starting amine **1.39** was transformed initially into the imine cyclo- $\text{C}_6\text{H}_{11}\text{-N=CH}_2$  **1.40** whose concentration remains low and almost constant throughout the reaction. A successive hydrogenation process converts **1.40** into the *N*-monomethyl derivative **1.41**, which is in turn transformed into the *N,N*-dimethyl product **1.42**. In this final step, no intermediates could be detected in solution by GC-MS. The total conversion of **1.39** to **1.42** is quantitative over a period of 6.5 hours. This method, while efficient for the *N*-alkylation of acyclic amines, is not applicable to the *N*-alkylation of arylamines.



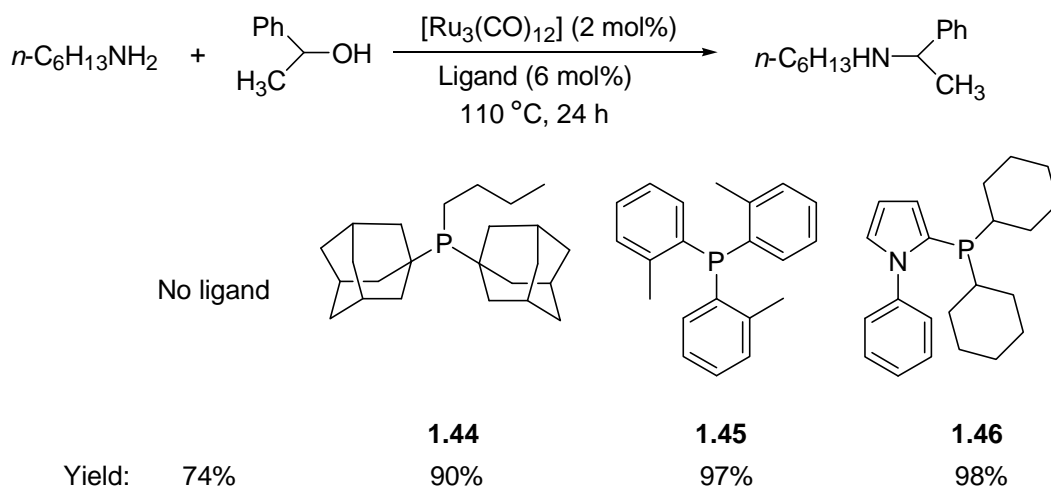
**Scheme 1.35** Stepwise formation of *N,N*-dimethylcyclohexylamine **1.42** from cyclohexylamine **1.39**.

Recently, Beller *et al.* investigated the *N*-alkylation of amines in the presence of different ruthenium catalysts generated *in situ*.<sup>[90-91]</sup> Different ruthenium precatalysts were tested including the Shvo catalyst **1.43** (Figure 1.6) and the ruthenium carbonyl cluster  $[\text{Ru}_3(\text{CO})_{12}]$  which catalysed the *N*-alkylation of *n*-hexylamine to a significant extent.



**Figure 1.6** Shvo catalyst **1.43**.

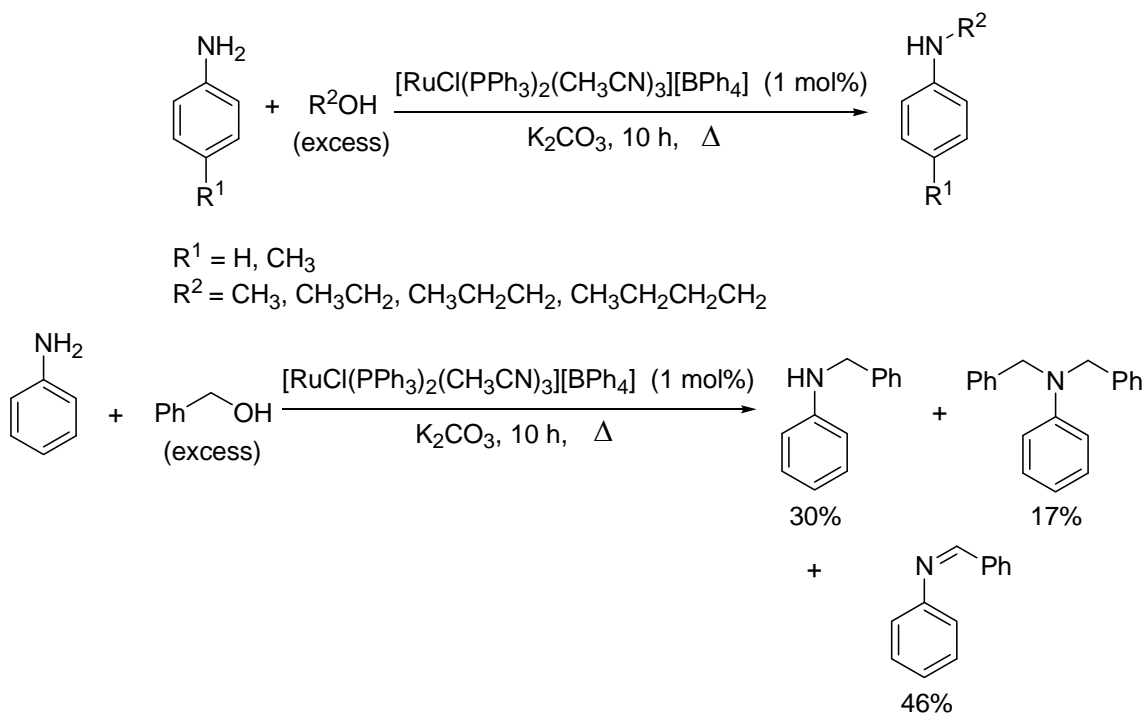
Subsequently, the ruthenium carbonyl cluster  $[\text{Ru}_3(\text{CO})_{12}]$  was tested in the presence of different phosphine ligands such as alkyl and aryl phosphines, ( $\pm$ )-Monophos, pyrrole phosphines as well as the Buchwald and Degussa type ligands. The reaction of *n*-hexylamine and 1-phenylethanol was chosen as a model reaction and among the ligands it was found that *n*-butyl-di-1-adamantyl-phosphine **1.44**, tri-*o*-tolylphosphine **1.45** and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole **1.46** gave the best conversions (Scheme 1.36).



**Scheme 1.36** *N*-Alkylation of *n*-hexylamine with 1-phenylethanol in the presence of  $[\text{Ru}_3(\text{CO})_{12}]$  and different ligands.

Bidentate ligands such as dppp and Xantphos were also tested but these ligands were found to inhibit the dehydrogenation of the alcohol and the hydrogenation of the imine. Hence, various primary and secondary alcohols were successfully coupled with primary amines in good to excellent yields including different heterocyclic alcohols such as 1-(2-furyl)ethanol and 2-thiophenylmethanol. However, no conversion was observed with aniline as the amine and this is presumably due to the reduced nucleophilicity. While this ruthenium carbonyl cluster is efficient, excess amounts (5 equiv.) of alcohol have to be employed in these reactions.

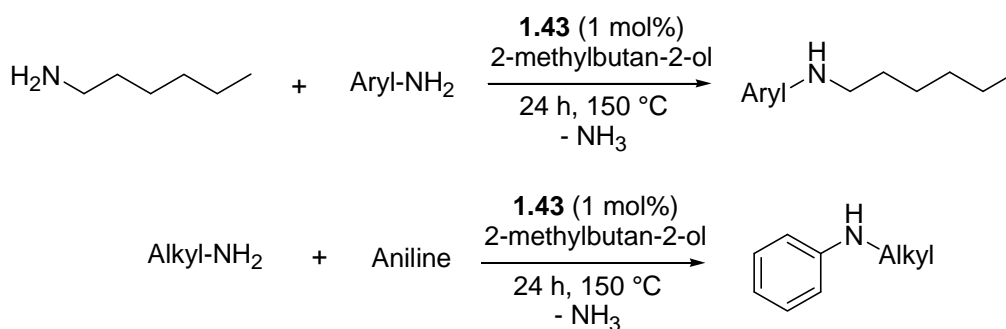
Also recently, Naskar and Bhattacharjee reported the selective *N*-monoalkylation of anilines catalysed by a cationic ruthenium(II) compound.<sup>[92]</sup> The group previously reported the synthesis and structure of the cationic ruthenium complex,  $[\text{RuCl}(\text{PPh}_3)_2(\text{CH}_3\text{CN})_3][\text{BPh}_4]$  which was found to be an effective catalyst for the transfer hydrogenation of aldehydes and ketones.<sup>[93]</sup> This cationic ruthenium(II) compound was also found to be effective for the selective reductive monoalkylation of aniline by primary alcohols.<sup>[92]</sup> Primary alcohols such as methanol are most suitable as alkylating agents but benzyl alcohol gave both mono- and dialkylated products along with the corresponding imine (Scheme 1.37). A possible mechanism for the reaction has been proposed to proceed through an imine intermediate.



**Scheme 1.37** *N*-Alkylation of aniline and aniline derivatives with cationic Ru(II) compound.

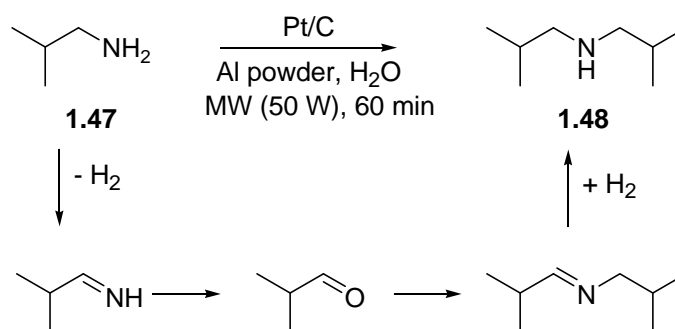
As an extension of this method, there are several reports in which primary amines undergo condensation. However, high hydrogen pressure is usually needed to carry out such condensations. A similar strategy has been reported by Beller *et al.* who recently developed the first arylation of aliphatic amines with anilines in the presence of the Shvo catalyst **1.43** (Figure 1.6) that proceeds under transfer hydrogenation conditions.<sup>[94]</sup>

Functionalised anilines and aliphatic amines were condensed to give the corresponding aryl amines in excellent yields (Scheme 1.38) and halogenated anilines and heterocyclic aminopyridine derivatives can also be easily synthesised. An advantage to this method is that there is no need for high-pressure equipment that is usually required for most reductive amination reactions.



**Scheme 1.38** *Synthesis of aromatic amines using Shvo catalyst 1.43 under transfer hydrogenation conditions.*

A related strategy has been reported by Miyazawa and co-workers whereby a catalytic amount of Pt/C and aluminium powder in water under microwave irradiation conditions can be used in the synthesis of secondary amines from primary amines.<sup>[95]</sup> The reaction is particularly applicable to amines bearing primary methylenes adjacent to amines as illustrated for the conversion of primary amine **1.47** into secondary amine **1.48** (Scheme 1.39). The mechanism is thought to proceed *via* oxidation of the amine into an imine. The imine is then hydrolysed to an aldehyde derivative as an intermediate and ammonia. The aldehyde reacts with the starting amine to give a new imine which subsequently gets reduced to a secondary amine. However, reactions with amines having secondary alkyl group tend to favour the formation of ketones while with other substrates produced tertiary amines as side products. It was found that water is not only a solvent but also a mediator for promoting the reactions.

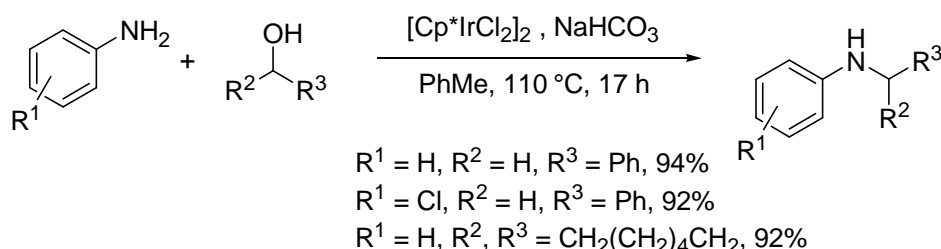


**Scheme 1.39** Reaction of amines with Pt/C in water under microwave irradiation.

Several iridium catalysts have been found to be effective catalysts for the *N*-alkylation reaction of amines with alcohols. Fujita, Yamaguchi and co-workers have described recent studies on the chemistry of  $\eta^5$ -pentamethylcyclopentadienyl (Cp\*) iridium complexes. The [Cp\*IrCl<sub>2</sub>]<sub>2</sub> catalyst was found to have high catalytic activities toward hydrogen transfer reactions including the Oppenauer-type oxidation of alcohols,<sup>[96]</sup> carbon-nitrogen bond formations,<sup>[70]</sup> and carbon-carbon bond formations.<sup>[97]</sup>

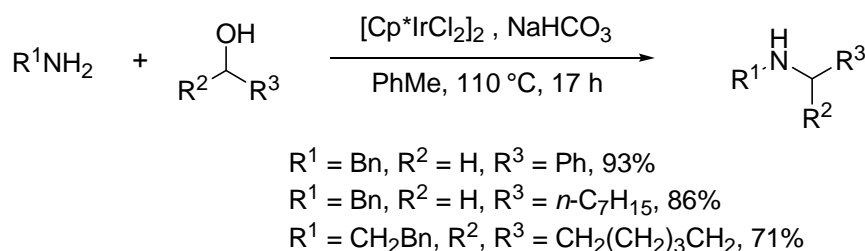
Hence, a full account of Cp\*Ir-catalysed *N*-alkylation of primary and secondary amines with primary and secondary alcohols has been reported by these co-workers. They have also described an example of the oxidative *N*-heterocyclisation of amino alcohols catalysed by this system leading to the synthesis of a variety of nitrogen heterocycles including indoles and hydroquinones.<sup>[88], [98]</sup>

The Cp\*Ir-catalysed *N*-alkylation of primary and secondary amines is carried out using equimolar amounts of the amine and alcohol in the presence of base. The group has described the optimised conditions for the reaction using the reaction of aniline with benzyl alcohol as a model reaction.<sup>[70]</sup> In the presence of NaHCO<sub>3</sub> as base, an excellent yield of 94% was obtained (Scheme 1.40). It was found that other weak bases such as Na<sub>2</sub>CO<sub>3</sub> and KHCO<sub>3</sub> were not as effective while strong bases such as Cs<sub>2</sub>CO<sub>3</sub> and NaO<sup>t</sup>Bu retarded the reaction. When the reaction was carried out without base, a low yield of 32% was obtained. With the optimised conditions, *N*-alkylation of anilines with various primary and secondary alcohols was carried out (Scheme 1.40) that resulted in high to excellent yields. A catalyst loading of 1 to 3 mol% was required, depending on the substrate. The same number of equivalents of NaHCO<sub>3</sub> as base was also required.<sup>[70], [99]</sup>



**Scheme 1.40** *N*-Alkylation of anilines with various primary and secondary alcohols.

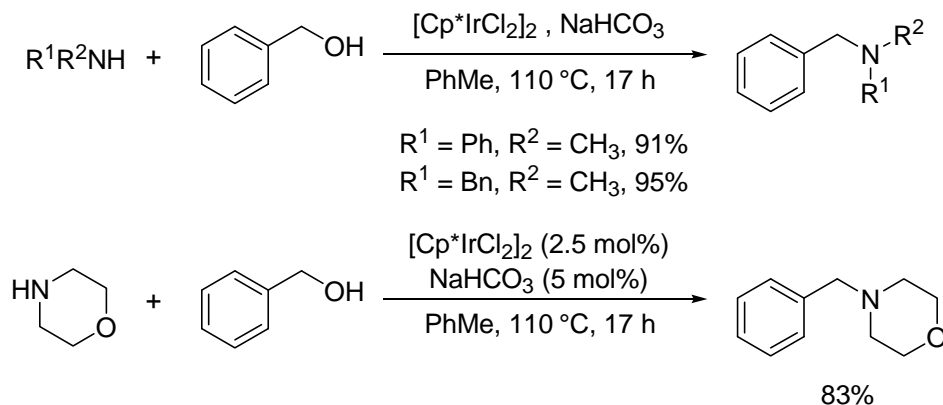
The *N*-alkylation of other primary amines such as benzylamine, phenethylamine and octylamine with primary and secondary alcohols proceeded in good to excellent yields.<sup>[70]</sup> A higher catalyst loading of 3 mol% Ir and higher temperatures were required for phenethylamine and octylamine respectively in order to obtain good yields (Scheme 1.41).



**Scheme 1.41** *N*-Alkylation of benzyl amines with various primary and secondary alcohols.

The *N*-alkylation of secondary amines was also investigated.<sup>[70]</sup> It was found that basicity and steric factors of amine substrates were crucial. The reaction of *N*-methylaniline with benzyl alcohol required higher catalyst loading (4 mol% Ir) to obtain an excellent yield while *N*-methylbenzylamine, a more basic and less sterically hindered

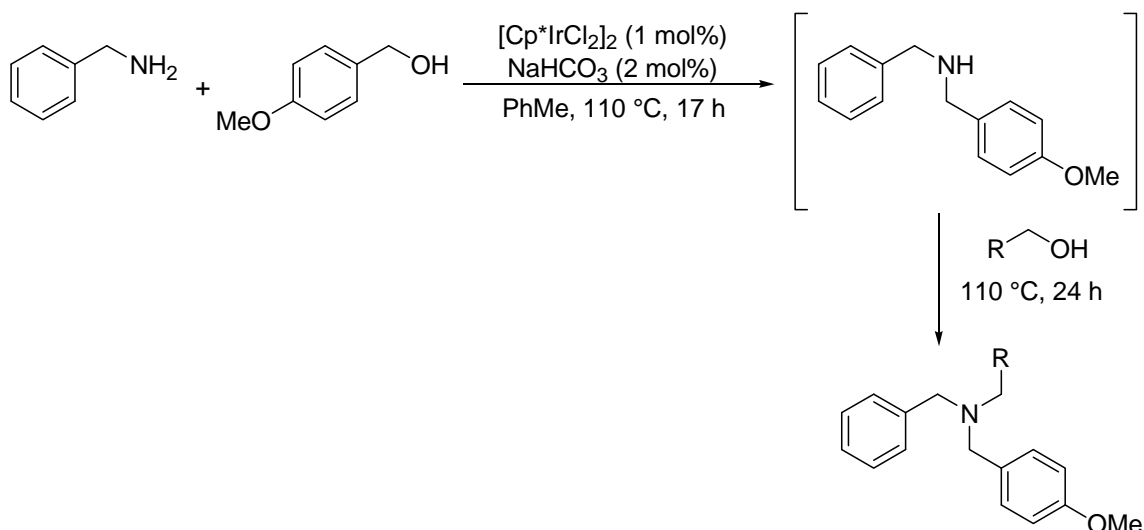
amine only needed 1 mol% Ir (Scheme 1.42). *N*-Isopropylbenzylamine resulted in a poor yield (<30%), highlighting the importance of steric encumbrance around the nitrogen of the amine. Other aliphatic and cyclic amines such as morpholine gave good to excellent yields.



**Scheme 1.42** *N*-Alkylation of secondary amines with benzyl alcohol.

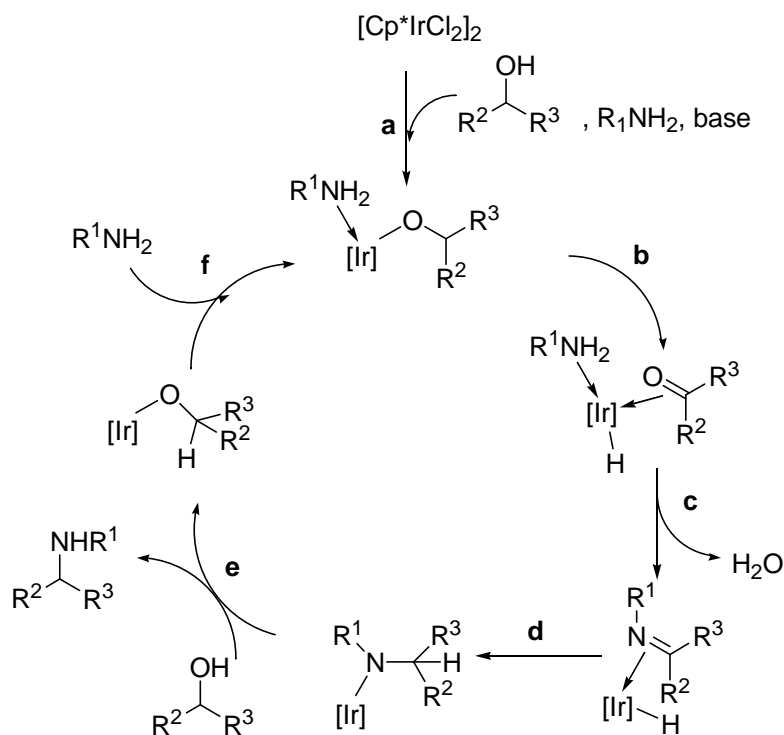
Similarly, the *N*-alkylation of other secondary amines with various primary and secondary alcohols was carried out.<sup>[70]</sup> The reaction of *N*-methylaniline with 1-octanol only gave 66% yield even after a higher catalyst loading of 5 mol% Ir and a higher temperature (130 °C) were employed. However, the reaction with other primary alcohols went smoothly and in some cases excess amounts of alcohols (2 equiv.) gave excellent results.

On the basis of the above experimental results, Fujita, Yamaguchi and co-workers developed a sequential addition of two different alcohols to the reaction system leading to the formation of tertiary amines bearing three different substituents.<sup>[70]</sup> Since the Cp\*Ir system is highly selective for mono-alkylation of primary amines, a subsequent addition of another alcohol to the mixture containing the first alkylated amine product led to the synthesis of a series of tertiary amines. Thus, by this methodology, several tertiary amines with different substituents were successfully synthesised (Scheme 1.43).<sup>[70]</sup>



**Scheme 1.43** One-pot sequential *N*-alkylation of benzylamine leading to the formation of tertiary amines.

The *N*-alkylation of amines is thought to proceed by the dehydrogenation of alcohols to aldehydes *via* hydrogen transfer from alcohol to an Ir complex, giving aldehyde and an Ir-hydride complex. This is followed by the formation of imines from aldehydes and amines and finally the hydrogenation of imines to amines. A possible mechanism for the Cp\*Ir-catalysed *N*-alkylation of primary amines with primary and secondary alcohols has been proposed (Scheme 1.44).<sup>[70]</sup>

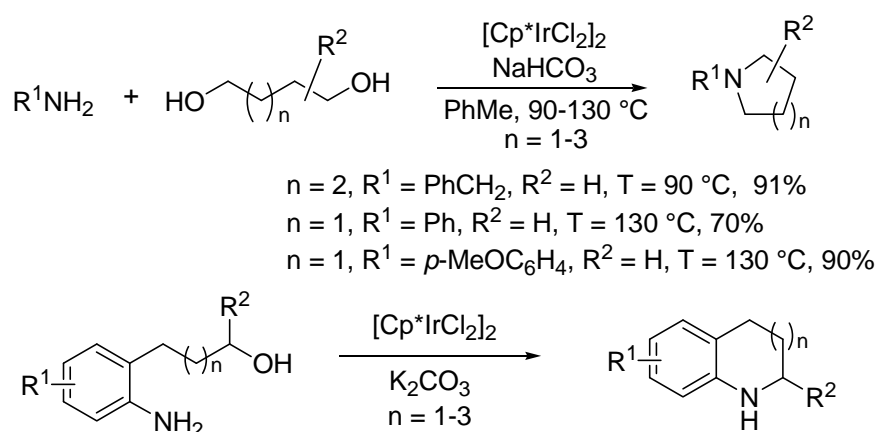


**Scheme 1.44** *N*-Alkylation of secondary amines with benzyl alcohol.



In the first step, the base initially would stimulate the formation of an iridium alkoxide species that would then coordinate with an amine (step a).  $\beta$ -Hydrogen elimination of the alkoxide moiety takes place forming an iridium hydride coordinated with the amine and aldehyde (or ketone) (step b). The imine-coordinated iridium hydride is formed from the condensation between the amine and the aldehyde (or ketone) in the coordination sphere of iridium (step c). Insertion of a C=N of the imine into iridium-hydride bond (step d) would take place, followed by amide-alkoxide exchange accompanied by the release of the product (step e). Finally, coordination of the amine (step f) would then occur to generate the catalytically active species. A closely similar mechanism has also been proposed for the  $\text{Cp}^*\text{Ir}$ -catalysed *N*-alkylation of secondary amines with primary and secondary alcohols.<sup>[70]</sup>

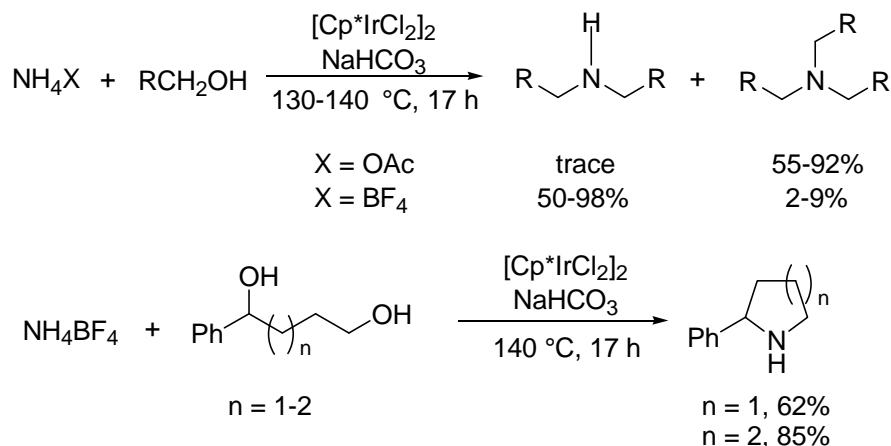
By a similar method, a variety of five-, six- and seven-membered cyclic amines was synthesised in good to excellent yields *via* the *N*-heterocyclisation of primary amines with diols catalysed by the same  $\text{Cp}^*\text{Ir}$  complex (Scheme 1.45).<sup>[100]</sup> Reactions of benzylamine with 1,4-butanediol, 1,5-butanediol and 1,6-hexanediol gave five-, six- and seven-membered cyclic amine in good to excellent yields. Aniline could also be used as the starting amine, but a higher catalyst loading (5 mol% Ir) and a higher temperature (130 °C) was required. However, the introduction of an electron-donating substituent such as a methoxy group at the phenyl ring of aniline improved the yield (Scheme 1.45).



**Scheme 1.45** Cyclisation of secondary amines with benzyl alcohol.

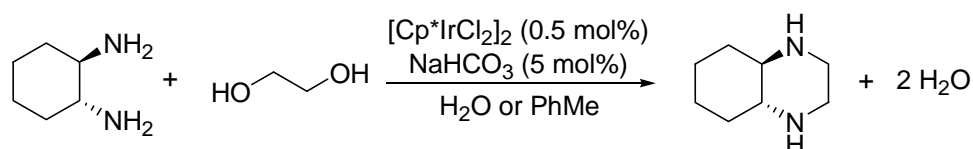
Also very recently, the efficient syntheses of secondary and tertiary amines have been described by Fujita, Yamaguchi and co-workers *via* the  $\text{Cp}^*\text{Ir}$ -catalysed multialkylation of ammonium salts with alcohols without solvent.<sup>[101]</sup> The selective synthesis of secondary and tertiary amines can be controlled by using the right ammonia

equivalents: the reactions of ammonium acetates with alcohols produced tertiary amines exclusively, while reactions with tetrafluoroborate gave secondary amines selectively. By this method, secondary five- and six-membered cyclic amines were also successfully synthesised from ammonium tetrafluoroborate and diols in one-pot (Scheme 1.46).



**Scheme 1.46** *Cp\*Ir-catalysed multialkylation of ammonium salts with alcohols or diols.*

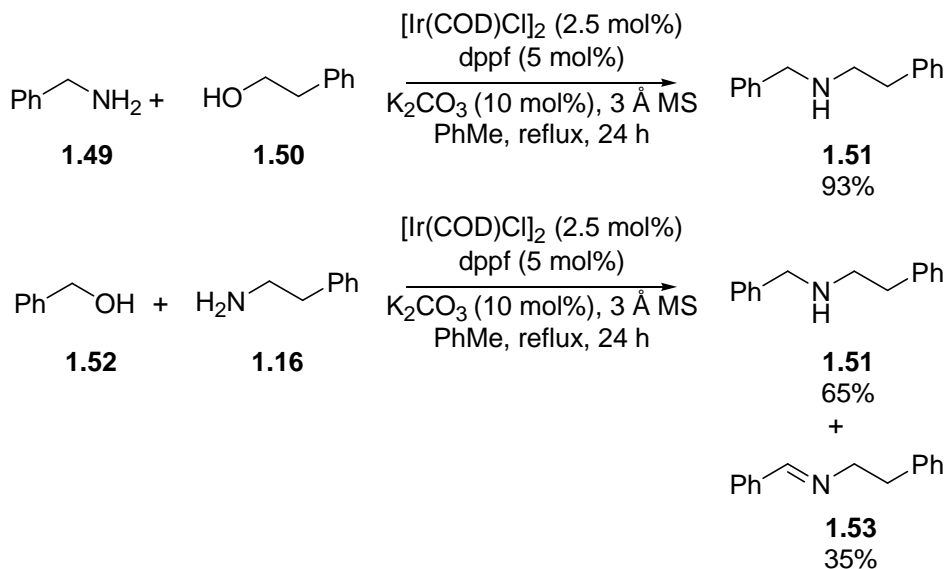
An extension to the use of trivalent iridium complex  $[\text{Cp}^*\text{IrCl}_2]_2$  as catalyst, Nordstrøm and Madsen employed this catalyst in the synthesis of piperazines by the cyclocondensation of diols and amines in aqueous media (Scheme 1.47).<sup>[102]</sup> Surprisingly, water is a highly effective solvent for the transformation since the reaction goes through two imines.  $\text{NaHCO}_3$  was chosen as the additive with either toluene or water as the solvent. The reactions were performed at moderate temperatures (100-120 °C) overnight, however, neat reactions require a high temperature of 160 °C to ensure full conversion but at a shorter time of 6 hours. Hence, a variety of substituted piperazines was synthesised in moderate to excellent yields by an iridium catalysed cyclocondensation of diols with either a primary amine or a 1,2-diamine (Scheme 1.46).



**Scheme 1.47** *Cp\*Ir-catalysed cycloaddition of diols and amines in aqueous media.*

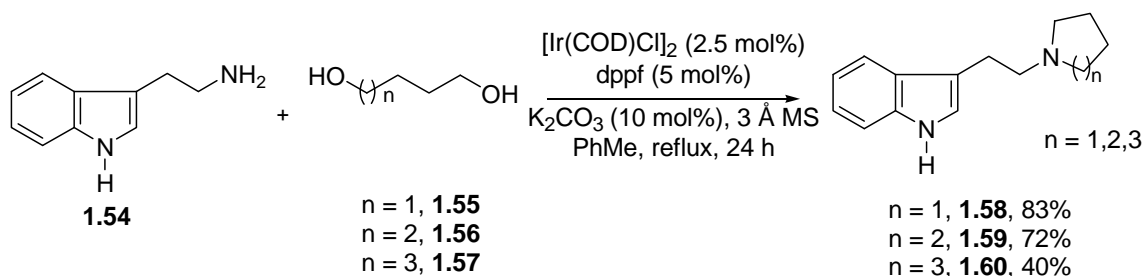
Williams *et al.* developed an efficient method for the *N*-alkylation of tryptamine and phenethylamine with alcohols as the alkylating agents.<sup>[103]</sup> Use of the iridium complex obtained from  $[\text{Ir}(\text{COD})\text{Cl}]_2$  combined with 1,1'-bis(diphenylphosphino)ferrocene (dppf) has been shown to be an effective catalyst for the transformation. The secondary

amine **1.51** was obtained in excellent yield from the alkylation of benzylamine **1.49** with phenethyl alcohol **1.50**. Conversely, the combination of phenethyl amine **1.16** with benzyl alcohol **1.52** led to the formation of the same product as well as the non-reduced imine **1.53** as by-product (Scheme 1.48).



**Scheme 1.48** *N*-Alkylation of amines with alcohols with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  as catalyst.

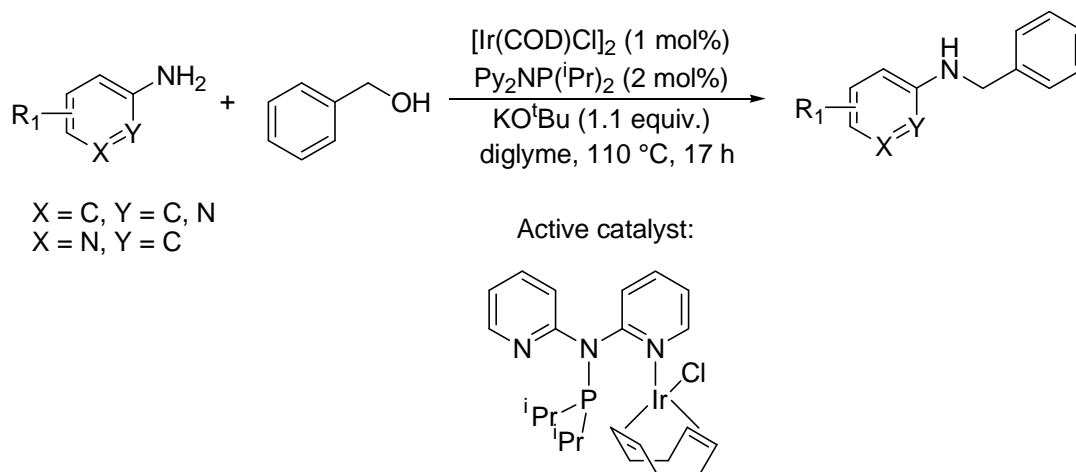
Additionally, under the same conditions, pyrrolidine **1.58**, piperidine **1.59** and azepane **1.60** were obtained in moderate to good yields from the reaction of tryptamine **1.54** with different diols (**1.55**, **1.56**, **1.57**) (Scheme 1.49).<sup>[103]</sup>



**Scheme 1.49** *N*-Heterocyclisation of primary amines with diol with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  as catalyst.

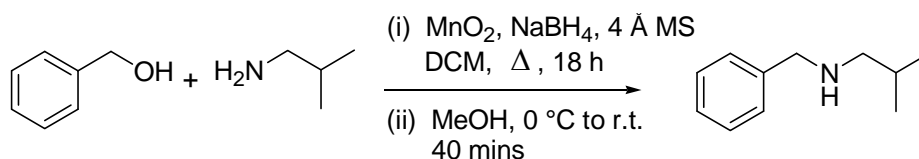
Also recently, Kempe and co-workers reported the synthesis of P-functionalised aminopyridine ligands and their iridium complexes as well as the catalytic activity of the catalyst towards the alkylation of primary aromatic and heteroaromatic amines with primary aromatic, heteroaromatic as well as aliphatic alcohols (Scheme 1.50).<sup>[73]</sup> A catalyst concentration of 1 mol%  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and 2 mol%  $\text{Py}_2\text{NP}(i\text{-Pr})_2$  was found to be optimal. Stoichiometric amounts of  $\text{KO}^t\text{Bu}$  as base were used in order to obtain the highest yields. To obtain the product quantitatively, an excess of 10% base is

necessary. Nevertheless, the process is highly selective towards monoalkylation and requires only moderate catalyst loadings.



**Scheme 1.50** Alkylation of primary aromatic and heteroaromatic amines with primary aromatic, heteroaromatic as well as aliphatic alcohols with an iridium complex.

Another strategy that involves a one-pot oxidation-imine formation-reduction sequence from alcohols to amines has been reported by Taylor and co-workers.<sup>[104]</sup> The steps are run individually and would essentially lead to the same outcome as the *N*-alkylation of amines with alcohols to form amines. The methodology uses stoichiometric amounts of oxidising agent (MnO<sub>2</sub>) and reducing agent (NaBH<sub>4</sub>) whereby both electron rich and electron deficient benzyl alcohol derivatives as well as unactivated alcohols were successfully employed as substrates. Primary amines were particularly good as starting substrates (Scheme 1.51).



**Scheme 1.51** One-pot oxidation-imine formation-reduction using manganese dioxide in the presence of sodium borohydride.

In conclusion, the *N*-alkylation of amines with alcohols is certainly a general method for the synthesis of amines. The [Cp\*IrCl<sub>2</sub>]<sub>2</sub>/NaHCO<sub>3</sub> catalytic system in particular is a versatile and highly atom economical method for the synthesis of amines. However, this method, while efficient for the *N*-alkylation of aromatic amines as well as aniline analogues with aromatic alcohols, has not been applied to the *N*-alkylation of simple aliphatic amines or the use of simple alcohols such as ethanol in these reactions. Furthermore, the catalyst is expensive and occasionally requires high temperatures, especially those that involve the *N*-heterocyclisation of primary amines (Scheme

1.45).<sup>[100]</sup> Thus, the search for a better and cheaper catalyst that is versatile in its reactions and requires milder conditions could be beneficial to the industrial synthesis of amines.

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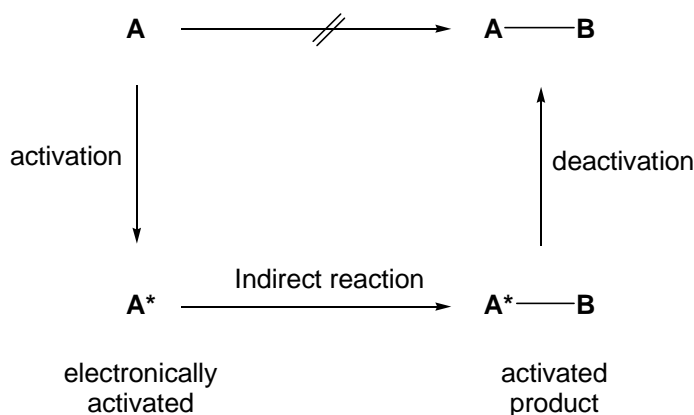
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## Chapter 2

### 2. Results and Discussion I

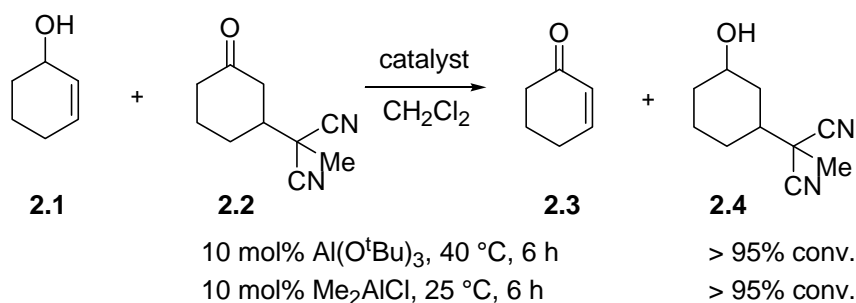
#### 2.1 Background

The concept of “catalytic electronic activation” has evolved from previous research by the Williams group which “temporarily enhances the electronic nature of a functional group to a given reaction”.<sup>[1,2]</sup> It was reasoned that if an unreactive substrate **A** could be temporarily activated electronically towards reaction (activated **A\***) then the desired bond formation could proceed indirectly with **A\*** to afford the activated intermediate **A\*–B**. The desired product **A–B** is formed by the return of **A\*–B** to the initial oxidation level.<sup>[3]</sup> This is depicted in Scheme 2.1.



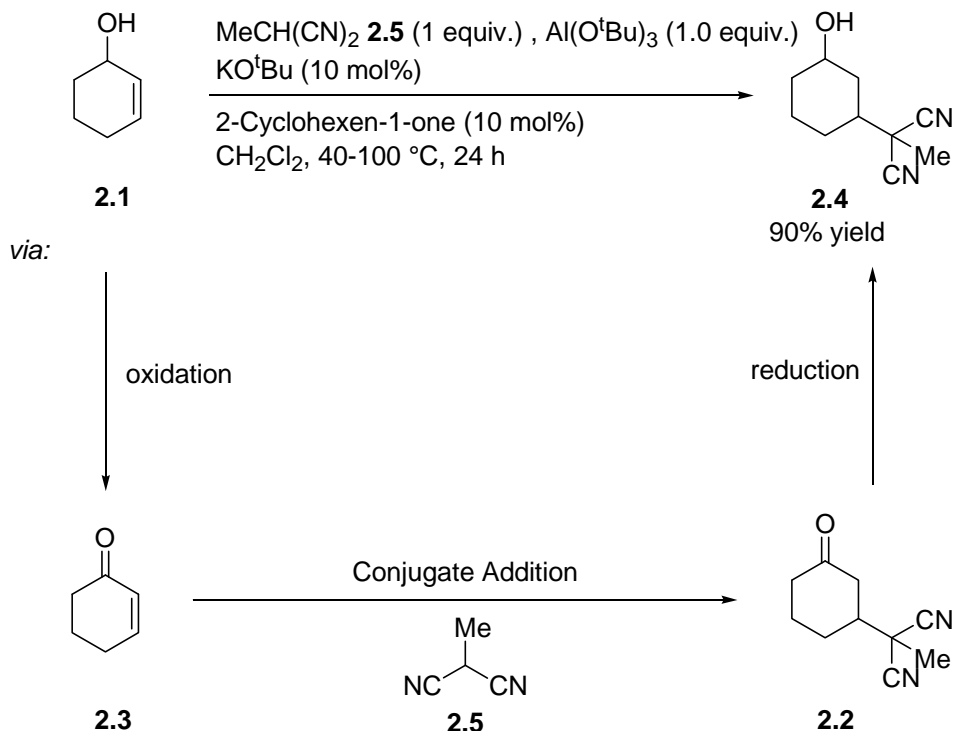
**Scheme 2.1** *Catalytic Electronic Activation.*

It started with the study of the ability of aluminium (MPV) catalysts to effect transfer hydrogenation between 2-cyclohexen-1-ol **2.1** and ketone **2.2** (Scheme 2.2).<sup>[1b]</sup>



**Scheme 2.2** *Oppenauer/MPV crossover.*

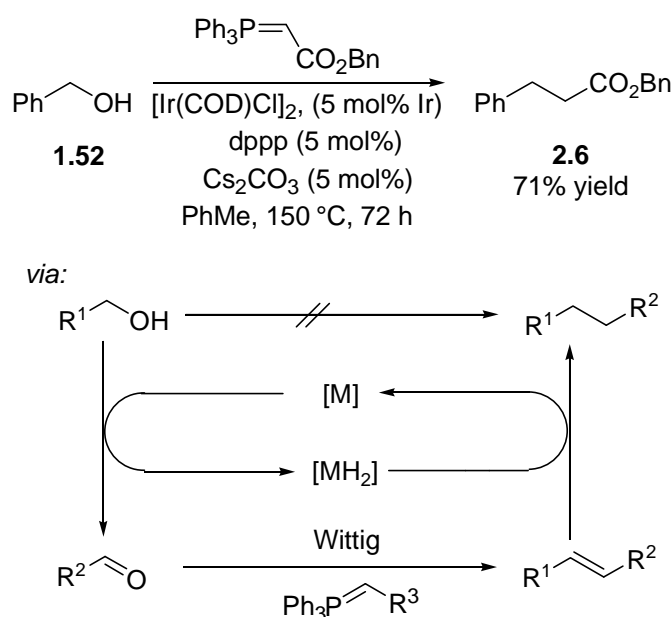
The results show that the equilibrium position for the transfer hydrogenation reaction lies firmly to the right, *i.e.* towards the thermodynamically more favourable conjugated ketone **2.3**.<sup>[1b]</sup> Based on these results, the principle was first applied to the indirect nucleophilic addition to allylic alcohols (Scheme 2.3).



**Scheme 2.3** Oppenauer/Michael addition/MPV process between **2.1** and **2.5**.

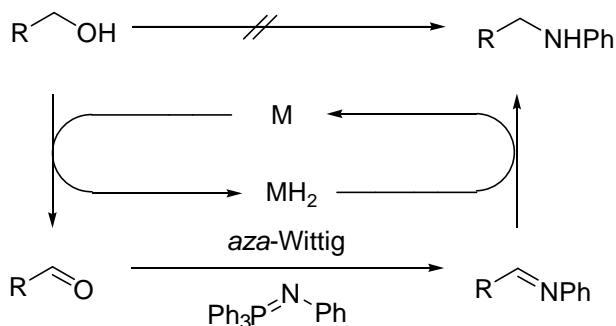
The concept of catalytic electronic activation is an attractive route to the formation of a new C-C bond.<sup>[4]</sup> As shown in Scheme 2.3, the unreactive allylic alcohol **2.1** is electronically activated to an  $\alpha,\beta$ -unsaturated ketone **2.3**. This electronically activated substrate would undergo a conjugate addition of methylmalononitrile **2.5** which is followed by a restoration of the alcohol functional group from **2.2** by transfer hydrogenation to give product **2.4**.<sup>[1]</sup> This was also successfully applied in the  $\beta$ -functionalisation of alcohols.<sup>[5,6]</sup> It was then necessary to develop a more general oxidation/reduction concept that would utilise a transition-metal catalyst that could function as a “hydrogen reservoir”, borrowing hydrogen from the substrate to initiate the reaction sequence and then returned in the final step. A wide range of functional groups could then be reduced without the need for external hydride donors and /or acceptors.<sup>[3]</sup>

The “borrowing hydrogen” strategy was applied in the C-C bond formation between alcohols *via* an indirect Wittig reaction (Scheme 2.4).<sup>[2]</sup> By this method, hydrogen atoms are borrowed during the *in situ* oxidation of the starting alcohol **1.52** to the corresponding aldehyde (metal-catalysed) and are subsequently returned in the hydrogenation of the alkene intermediate formed by the Wittig olefination of the aldehyde to give product **2.6**. In comparison to most transfer hydrogenation reactions, only one equivalent of the alcohol is required.<sup>[7]</sup> This system is unique in that there is no net oxidation transformation because the hydrogen is borrowed temporarily.<sup>[3]</sup>



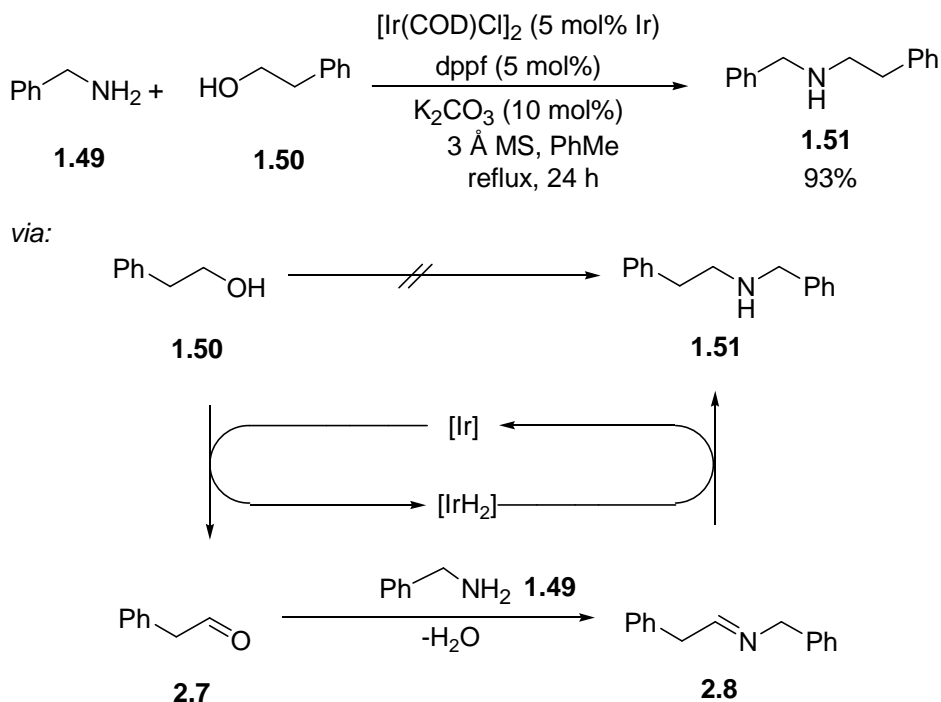
**Scheme 2.4** Indirect Wittig reaction of alcohols by “borrowing hydrogen”.

These preliminary findings were reported in 2002 by Williams *et al.* and subsequently an improved ruthenium-catalysed system that proceeded under milder conditions was reported by the group.<sup>[2]</sup> The concept of “borrowing hydrogen” has also been applied to the formation of C-N bonds *via aza*-Wittig and imine chemistry (Scheme 2.5).<sup>[8]</sup> Similarly, hydrogen is temporarily removed from the alcohol to give an intermediate aldehyde which then undergoes an *aza*-Wittig reaction with the iminophosphorane to afford the imine. Subsequently, the hydrogen is returned by the catalyst reducing the imine to an amine.



**Scheme 2.5** Indirect aza-Wittig reaction of alcohols in the synthesis of amines by “borrowing hydrogen”.

Although this method was successful in the synthesis of  $\beta$ -aminoarenes, the removal of triphenylphosphine during the reactions was found to be difficult. Since imines are readily formed by the reaction between an aldehyde or ketone with an amine with the azeotropic removal of water, it was then proposed to use free amines instead of iminophosphorane. Indeed this was plausible because the use of molecular sieves enabled these reactions to achieve higher yields (Scheme 2.6).<sup>[9]</sup>



**Scheme 2.6** Indirect N-alkylation of amines by “borrowing hydrogen”.

By this method, a simple strategy for the N-alkylation of tryptamine and phenethylamine was developed (Scheme 1.50, Chapter 1) that involves the direct condensation between an amine and an alcohol. As shown in Scheme 2.6, the reaction proceeds by catalytic activation, involving an iridium catalyst which activates phenethyl alcohol **1.50** by “borrowing hydrogen” to provide aldehyde **2.7** which undergoes reductive amination to

**2.8.** Subsequently, the hydrogen is returned by the catalyst reducing the imine **2.8** (or iminium salt) to the amine product **1.51**. There is no net oxidation or reduction during the catalytic cycle, but the temporary removal of hydrogen is required in order for the reaction to go.<sup>[9]</sup>

It was then proposed that the use of diols with primary amines should lead to the formation of *N*-heterocycles. There is a procedure in the literature for this reaction but forcing conditions are required<sup>[10]</sup> and at the time of the discovery of this iridium system<sup>[9]</sup> Yamaguchi *et al.* reported the *N*-heterocyclisation of primary amines with diols using a Cp\*Ir catalyst (Scheme 1.45, Chapter 1).<sup>[11]</sup> Using [Ir(COD)Cl]<sub>2</sub> under the same conditions, some examples of *N*-heterocyclisation have been performed utilising diols as the substrate (Scheme 1.49, Chapter 1).<sup>[9]</sup>

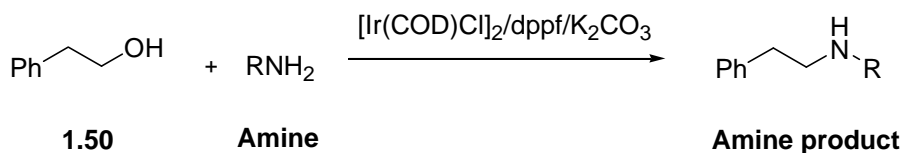
## 2.2 Research Goals

As described in Chapter 1, there are several ruthenium catalysts that have precedent in the literature<sup>[10, 12]</sup> which describe the *N*-alkylation of amines but high temperature conditions are usually required. Although much work has been carried out in the *N*-alkylation of amines involving iridium catalysts (*vide supra*), the search for an improved catalyst that is versatile in its reactions and requires milder conditions could lead to a major impact in the synthesis of amines by industry. With this basis, the objectives of this research effort include the following goals:

1. To find a more efficient catalytic system for the *N*-alkylation of amines by “borrowing hydrogen” and hence optimise its conditions.
2. To investigate the application of the optimised catalytic system in the synthesis of a variety of amines and biologically active amines.

### 2.3 Iridium-Catalysed *N*-Alkylation of Amines with Phenethyl Alcohol by Borrowing Hydrogen

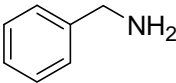
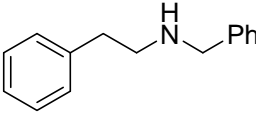
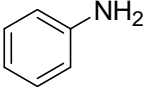
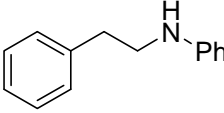
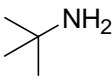
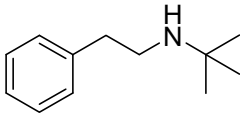
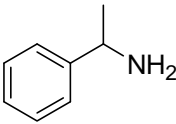
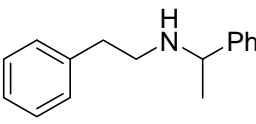
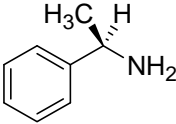
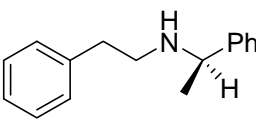
The  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  system was known to be an efficient system for the *N*-alkylation of benzylamine and phenethylamine (Scheme 2.6 and 1.50, Chapter 1) by “borrowing hydrogen” before we embarked on an investigation to optimise the *N*-alkylation of a range of amine substrates. As an extension of the indirect formation of amines from alcohols, we wanted to see the scope of the reaction in terms of the different types of amines that could be used *via* the “borrowing hydrogen” methodology (Scheme 2.7). It is important to note that phenethyl alcohol is chosen as the starting alcohol as it would lead to the formation of phenethylamine derivatives that possess physiological and psychological properties described earlier (Section 1.1). The phenethylamine product could easily be detected by the presence of a multiplet belonging to the phenethyl protons at the region of  $\delta 2$  to  $\delta 3$  ppm in the  $^1\text{H}$  NMR spectrum of the crude mixture. Therefore, the reaction of phenethyl alcohol **1.50** and benzylamine **1.49** was repeated under the same  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  conditions reported by the group<sup>[9]</sup> along with several amines and the results are summarised in Table 2.1.



**Scheme 2.7** Reaction of phenethyl alcohol and different primary amines under  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  conditions.



**Table 2.1** Reaction of phenethyl alcohol and different primary amines under [Ir(COD)Cl]<sub>2</sub>/dppf/K<sub>2</sub>CO<sub>3</sub> conditions .

$  \begin{array}{ccc}  \text{Ph-CH}_2\text{-CH}_2\text{-OH} & + & \text{RNH}_2 \\  \text{1.50} & \text{Amine} & \\  \end{array}  \xrightarrow[\text{3 \AA MS, PhMe, reflux, 24 h}]{\begin{array}{c} [\text{Ir}(\text{COD})\text{Cl}]_2 \text{ (5 mol\% Ir)} \\ \text{dppf (5 mol\%)} \\ \text{K}_2\text{CO}_3 \text{ (10 mol\%)} \end{array}}  \begin{array}{c} \text{Ph-CH}_2\text{-CH}_2\text{-N(H)-R} \\ \text{Amine product} \end{array}  $			
Entry <sup>[a]</sup>	Starting amine	Product	Yield (%) <sup>[b]</sup>
1	 <b>1.49</b>	 <b>1.51</b>	72 (88)
2	 <b>2.9</b>	 <b>2.10</b>	59
3	 <b>2.11</b>	 <b>2.12</b>	35 (52)
4	 <b>2.13</b>	 <b>2.14</b>	21 (30)
5	 <b>2.15</b>	 <b>2.16</b>	35 (59)

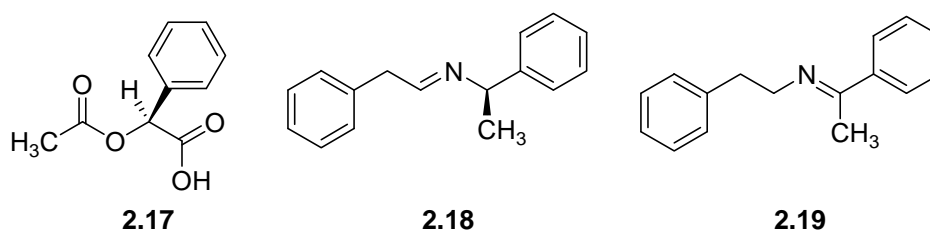
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

[b] Isolated yields after column chromatography. The values in parentheses refer to conversions as determined by <sup>1</sup>H NMR analysis.

A modest yield of 72% (88% conv.) of product **1.51** was obtained for the reaction of alcohol **1.50** and benzylamine **1.49** as compared to the reported yield of 93%<sup>[9]</sup> (Table 2.1, entry 1). Other amines used in the reaction included aniline **2.9** and *t*-butylamine **2.11** but only moderate to low yields were obtained (Table 2.1, entries 2 and 3). We also examined the possibility of the synthesis of the enantiomerically enriched

phenethylamine derivative **2.16** by the  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  catalytic system (Table 2.1, entries 4 and 5).

The investigation started with the *N*-alkylation reaction of racemic ( $\pm$ )- $\alpha$ -methylbenzylamine **2.13** and after the isolation of ( $\pm$ )-phenethyl-(1-phenylethyl)amine **2.14** by column chromatography, it was subjected to separation of the enantiomers by HPLC. After several attempts to separate them by this method failed, an analysis of enantiomers by a resolving agent was carried out. (*S*)-Acetylmandelic acid **2.17** was used according to the procedure described in the literature<sup>[13]</sup> and proved to be a suitable method of distinguishing between the mixtures whereby two doublets at  $\delta$ 1.3-1.4 in its  $^1\text{H}$  NMR spectrum were obtained which referred to the methyl group of the amine product. This investigation was important as it would be useful in the same reaction with (*R*)-(+)- $\alpha$ -methylbenzylamine **2.15**.

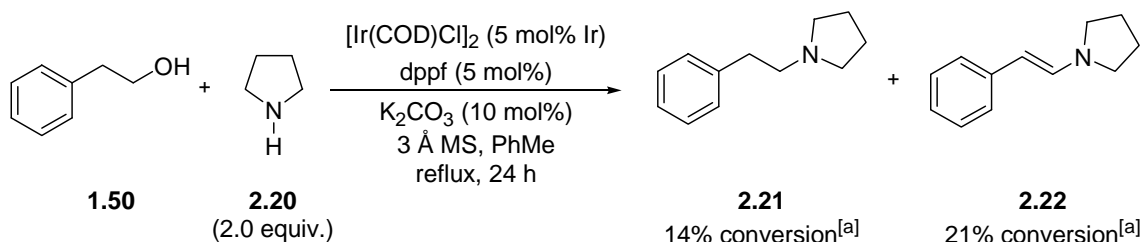


**Figure 2.1** Structures of (*S*)-acetylmandelic acid **2.17** and intermediate imines formed between **1.50** and **2.15**.

(*S*)-Acetylmandelic acid **2.17** was added to the isolated (*R*)- $\alpha$ -phenethyl-(1-phenylethyl)amine **2.16** and we were delighted to find the quartets at the  $\delta$ 3.8-4.0 region had a ratio of 33:1 which indicated that there was a retention of configuration in the product amine (94% ee). This implies that the intermediate imine during this transfer hydrogenation is imine **2.18** and not **2.19** and that no other racemisation process is involved. This is a useful result since to our knowledge, the synthesis of amine **2.16** by this method has not been reported before.

In order to investigate further the variety of amines that would undergo the *N*-alkylation process under the  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  catalytic conditions, we decided to perform the reaction with benzamide instead of the amine but the  $^1\text{H}$  NMR spectrum was difficult to interpret. Pyrrolidine **2.20** which is a secondary amine was also subjected to the same iridium conditions and we were pleased to find that the desired product **2.21** was obtained in a 14% conversion by analysis of the  $^1\text{H}$  NMR spectrum. However, this low conversion was obtained presumably due to the presence of the unreduced enamine

**2.22** that was also detected in the  $^1\text{H}$  NMR spectrum of the crude product (Scheme 2.8). A doublet at  $\delta 5.0$  ppm confirmed this deduction which indicated the presence of an alkenyl carbon ( $=\text{CH}$ ) of enamine **2.22** with a conversion of 21%.



**Scheme 2.8** Reaction of phenethyl alcohol **1.50** and pyrrolidine **2.20** under  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  conditions. [a] Conversion determined by  $^1\text{H}$  NMR analysis.

On the basis of these results, the *N*-alkylation of amines with alcohols under the  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{dppf}/\text{K}_2\text{CO}_3$  conditions was found to be suitable for primary amines by “borrowing hydrogen”. However, the reaction seemed to be highly efficient for benzylamine and only moderately efficient for other amines such as *t*-butylamine and methylbenzylamine. Therefore, we needed to investigate the possibility of a more efficient system that is versatile in its reactions and optimise its conditions.

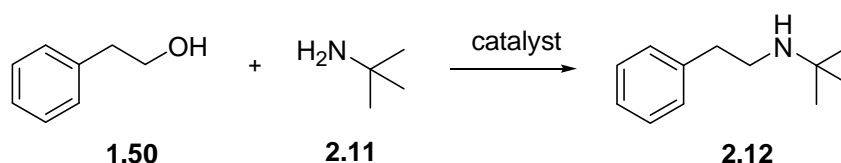
## 2.4 Ruthenium-Catalysed *N*-Alkylation of Primary Amines with Primary Alcohols by Borrowing Hydrogen

Fujita *et al.* have reported an efficient catalytic system for the *N*-alkylation of amines with alcohols that utilises a  $\text{Cp}^*\text{Ir}$  complex<sup>[14]</sup> in the synthesis of secondary and tertiary amines already described extensively in Chapter 1. While this catalyst is highly active and atom-efficient, it would not be applicable on a large industrial scale due to its cost. As described by Blaser *et al.*, many catalyst precursors and ligands are very expensive, therefore the search for cheaper catalysts with the same performance is necessary in terms for the industrial application of homogeneous catalysts (Ir catalyst is no exception).<sup>[15]</sup> We became interested in a ruthenium-based homogeneous catalytic systems for several reasons, namely: (i) ruthenium catalysts are usually relatively cheaper than other transition metal catalysts such as iridium and rhodium,<sup>[16]</sup> (ii) there is a whole variety of oxidative systems centred around ruthenium catalysts and they are mostly commercially available,<sup>[17]</sup> (iii) ruthenium catalysts are compatible with many ligands and hence there is a large scope for manipulating the complexes. Additionally, we discovered that there is no efficient catalyst besides the  $[\text{CpRuCl}(\text{PPh}_3)_2]$  introduced by Del Zotto *et al.* which was only limited to the *N*-methylation with methanol.<sup>[18]</sup> The

Williams group have also recently reported that ruthenium complexes in the presence of bidentate phosphines are particularly effective for the formation of C-C bonds from alcohols with the reactions similarly proceeding *via* intermediate carbonyl compounds.<sup>[19]</sup>

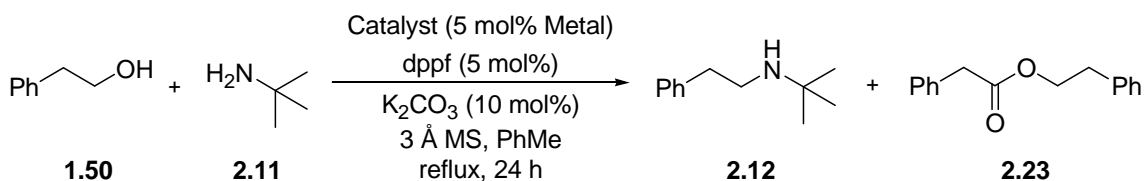
Encouraged by the results obtained from the *N*-alkylation of amines with alcohols under the [Ir(COD)Cl]<sub>2</sub>/dppf/K<sub>2</sub>CO<sub>3</sub> conditions, we chose to explore other potentially efficient catalytic systems by “borrowing hydrogen” that are ruthenium-based in particular.

Our investigation started with the alkylation of *t*-butylamine **2.11** with phenethyl alcohol **1.50** as a model reaction (Scheme 2.9). Once again we were particularly interested in the synthesis of phenethylamine derivatives due to the range of neurotransmitters, and their agonists and antagonists possessing this structure. We also found that *t*-butylamine **2.11** was the ideal amine for our model reaction since it is low boiling and therefore led to easy identification of potential amine product in the crude mixture. Additionally, isolation of pure amine **2.12** only required the use of diethyl ether as the eluent in purification by column chromatography.



**Scheme 2.9** *N*-Alkylation of amine **2.11**.

The first screening was based on the [Ir(COD)Cl]<sub>2</sub>/dppf/K<sub>2</sub>CO<sub>3</sub> combination whereby the *N*-alkylation reaction of **2.11** with alcohol **1.50** was carried out in the presence of various catalysts and dppf as the ligand and K<sub>2</sub>CO<sub>3</sub> as the activating base (Table 2.2).

**Table 2.2** Results for catalyst screening for the reaction of phenethyl alcohol **1.50** and *t*-butylamine **2.11**.

Entry <sup>[a]</sup>	Catalyst	Amine <b>2.12</b> (%) <sup>[b]</sup>	Ester <b>2.23</b> (%) <sup>[b]</sup>
1	[Ir(COD)Cl] <sub>2</sub>	54	6
2	[Ru(OAc)] <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub>	0	9
3	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	0	0
4	[Ru(CO)(PPh <sub>3</sub> ) <sub>3</sub> H <sub>2</sub> ]	0	26
5	[Ru(PPh <sub>3</sub> ) <sub>3</sub> Cl <sub>2</sub> ]	35	0
6	[Ru(C <sub>6</sub> H <sub>6</sub> )Cl <sub>2</sub> ] <sub>2</sub>	84	16
7	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub>	100	0
8	[Cp*IrCl <sub>2</sub> ] <sub>2</sub>	15	0

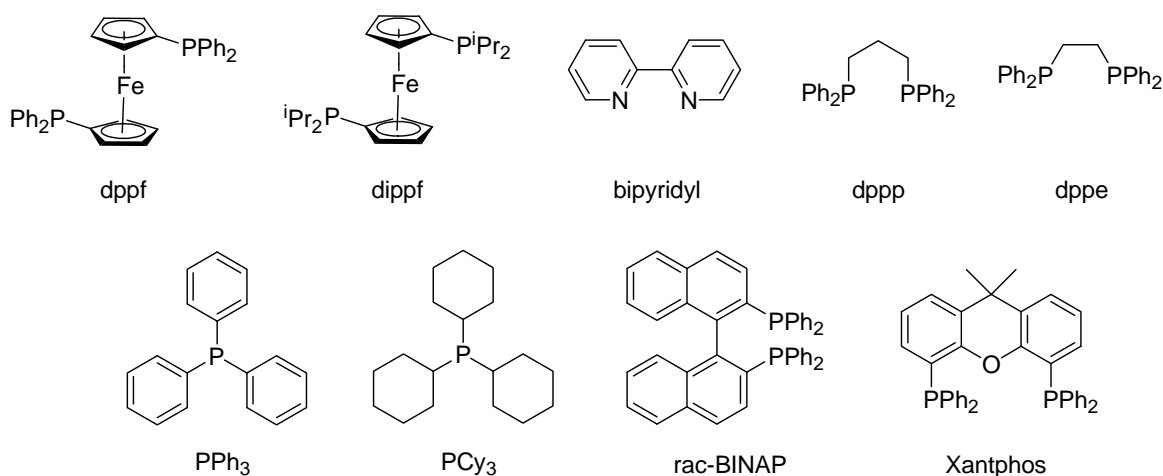
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

[b] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

As expected, [Ir(COD)Cl]<sub>2</sub>/dppe system gave 54% conversion into the amine product and a small amount of ester **2.23** (Table 2.2, entry 1) (*vide infra*). [Ru(OAc)]<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub> as well as [Cp\*RhCl<sub>2</sub>]<sub>2</sub> were ineffective in the *N*-alkylation reaction as indicated in entries 2 and 3. The combination of dppe and [Ru(CO)(PPh<sub>3</sub>)<sub>3</sub>H<sub>2</sub>] was unsuccessful for this reaction, despite its use in C-C bond formation<sup>[19]</sup> but it had some activity towards the formation of ester **2.23**. This is presumably formed from the addition of alcohol to the intermediate alcohol and followed by the oxidation of the so-formed hemi-acetal (Table 2.2, entry 4).<sup>[20]</sup>

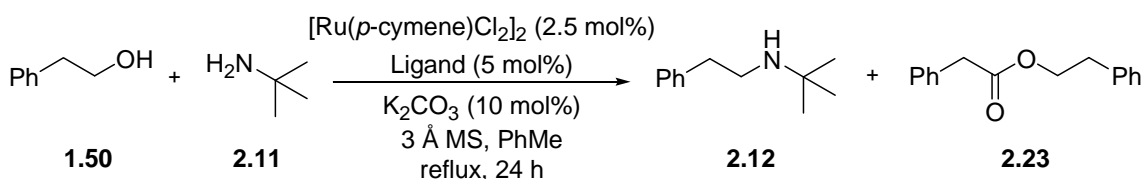
[Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub>]/dppe gave some product as well as the other three catalysts (Table 2.1, entries 5-8) but the combination of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and dppe appeared to be the most effective in this reaction (Table 2.1, entry 7). Taking the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>/dppe combination, we decided to explore its activity with different phosphine ligands (Figure

2.2) in order to determine a trend of reactivity for the different ligands (Table 2.3). It is important to note that 1 mole of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  provides two moles of ruthenium atoms.



**Figure 2.2** Phosphine and pyridyl ligands employed in initial ligand screening.

Figure 2.2 shows the structures of phosphine and pyridyl ligands used in initial ligand screening. The results show the nature of the ligands, *i.e.* ligand bite angles for the bidentate phosphine ligands or cone angles for monophosphine ligands have no positive correlation between bite angle<sup>[21]</sup> (or cone angle<sup>[22]</sup>) and selectivity for amine product.

**Table 2.3** Results for ligand screening for the reaction of phenethyl alcohol **1.50** and *t*-butylamine **2.11**.

Entry <sup>[a]</sup>	Ligand	Amine <b>2.12</b> (%) <sup>[b]</sup>	Ester <b>2.23</b> (%) <sup>[b]</sup>
1	none	0	8
2	dppf	100	0
3	dippf	80	20
4	2,2'-Bipyridine	0	1
5	dppp	52	6
6	dppe	20	0
7	$\text{PPh}_3$ (10 mol%)	36	10
8	$\text{PCy}_3$ (10 mol%)	0	10
9	Xantphos	39	61
10	<i>rac</i> -BINAP	35	53

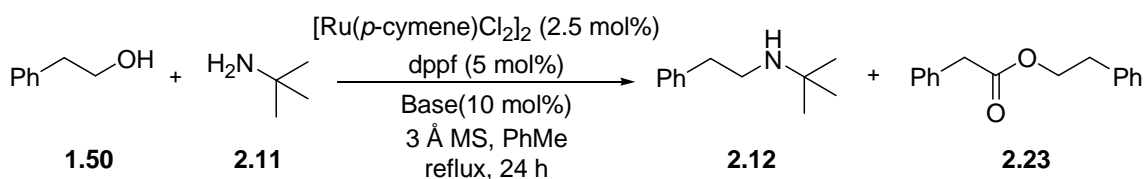
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

[b] Conversions are based on alcohol and are determined by  $^1\text{H}$  NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  was found to be inactive in the absence of a ligand (Table 2.3, entry 1).  $\text{PCy}_3$  and 2,2'-bipyridine as ligand in this reaction were found to be ineffective (Table 2.3, entries 4 and 8), whilst dppp and  $\text{PPh}_3$  gave some amine product and a small amount of the ester (Table 2.3, entries 4 and 8). Dppe was selective for the formation of amine product but the conversion is low (Table 2.3, entry 6). Xantphos and BINAP showed encouraging results but Xantphos with the largest bite angle gave an appreciable amount of ester product too (Table 2.3, entries 9 and 10). This indicated that the amination and ester formation reactions were competing against each other under these conditions. Dippf appeared to be an effective ligand in this catalytic process but this ligand is more expensive than dppf and therefore would be less cost

effective (Table 2.3, entry 3). Hence, from all of the ligands examined, dppf is therefore the most effective ligand for this transformation and hence the ligand of choice for further optimisation studies. Subsequently, the effect of different bases as well as the influence of catalyst/K<sub>2</sub>CO<sub>3</sub> ratio was then carried out using the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>/dppf combination (Table 2.4).

**Table 2.4** Results for base screening for the reaction of phenethyl alcohol **1.50** and *t*-butylamine **2.11**.



Entry <sup>[a]</sup>	Base	Ru:K <sub>2</sub> CO <sub>3</sub>	Amine <b>2.12</b> (%) <sup>[b]</sup>	Ester <b>2.23</b> (%) <sup>[b]</sup>
1	KO <sup>t</sup> Bu	1:1	2	31
2	Cs <sub>2</sub> CO <sub>3</sub>	1:1	6	27
3	Na <sub>2</sub> CO <sub>3</sub>	1:1	77	3
4	Li <sub>2</sub> CO <sub>3</sub>	1:1	83	2
5	K <sub>2</sub> CO <sub>3</sub>	1:1	96	4
6	K <sub>2</sub> CO <sub>3</sub>	1:0.8	96	4
7	K <sub>2</sub> CO <sub>3</sub>	1:2.0	57	0
8	No Base	-	96	4
9	K <sub>2</sub> CO <sub>3</sub>	No catalyst	0	0

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

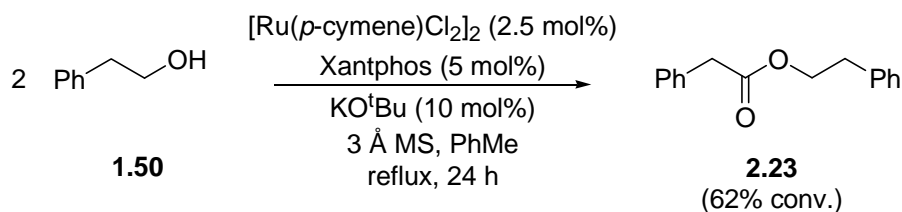
[b] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

The results of these reactions show KO<sup>t</sup>Bu and Cs<sub>2</sub>CO<sub>3</sub> are inactive for the reaction but favour the formation of the ester (Table 2.4, entries 1 and 2) whilst Na<sub>2</sub>CO<sub>3</sub> and Li<sub>2</sub>CO<sub>3</sub> are both suitable as base but the reaction did not go to completion (Table 2.4, entries 3 and 4). Having less base (Ru:K<sub>2</sub>CO<sub>3</sub> = 1:0.8) than catalyst had a slight selectivity towards the ester (Table 2.4, entry 6) but with double the amount of base stopped the formation of ester but retarded the formation of the amine product (Table 2.4, entry 7).



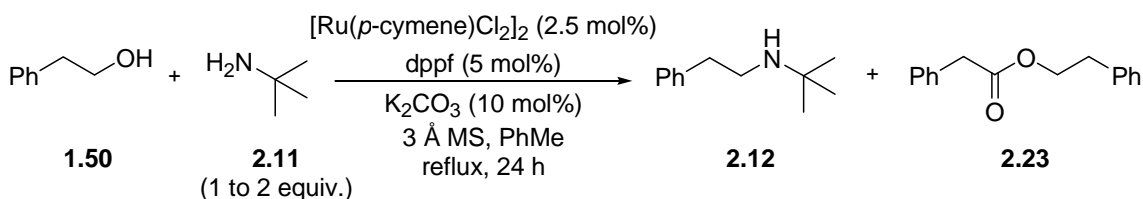
It is interesting to discover that without the presence of base, the reaction also went almost to completion (Table 2.4, entry 8) and presumably the *t*-butylamine being quite basic ( $pK_a$  of  $t\text{BuNH}_3^+ = 10.55$ ) acts as a base in the catalytic cycle. Entry 9 acts as a control which proves that the catalyst is an important factor for the *N*-alkylation reaction to occur.

Xantphos as ligand and  $\text{KO}^t\text{Bu}$  as base with  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  as catalyst appear to favour the condensation of the starting alcohol leading to the formation of ester (Table 2.3, entry 9 and Table 2.4, entry 1). Attempts to extend the scope of the reaction in order to investigate how much ester would be formed in a reaction by using these parameters were carried out (Scheme 2.10). Disappointingly, a moderate conversion of 65% determined by  $^1\text{H}$  NMR analysis was obtained. Nevertheless, upon optimisation of the reaction using this catalytic system could potentially lead to the selective synthesis of ester **2.23** since use of this catalytic system has not been reported before.



**Scheme 2.10** Synthesis of ester **2.23** employing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ /xantphos catalytic system with  $\text{KO}^t\text{Bu}$  as base.

In a next step towards optimising the  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}$  catalytic system, the influence of the alcohol:amine ratio was examined in order to determine any reduced effect on the ester formed (Table 2.5).

**Table 2.5** Results for screening for alcohol:amine ratio for the reaction of phenethyl alcohol **1.50** and *t*-butylamine **2.11**.

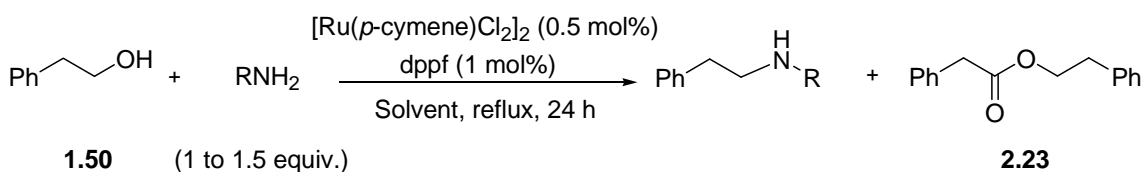
Entry <sup>[a]</sup>	Alcohol:Amine	Amine <b>2.12</b> (%) <sup>[b]</sup>	Ester <b>2.23</b> (%) <sup>[b]</sup>
1	1:1	96	3
2	1:1.2	96	4
3	1:1.5	98	2
4	1:2.0	85	2

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine according to ratio given, 3 Å MS, 110 °C, 24 h.

[b] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

The results of these reactions show that ester formation was still obtained despite having excess amount of starting amine in the reaction (Table 2.5, entries 1-4). In fact, by having a one-fold excess of the amine had a negative effect and 13% unreacted starting alcohol **1.50** was recovered (Table 2.5, entry 4). Because the results varied significantly, we repeated the experiments at different alcohol:amine ratios with more dilute reaction conditions (2.5 mL of solvent as opposed to the normal 1 mL of solvent). Having almost optimised the reaction conditions, it was also of interest to know whether the amount of catalyst could be reduced without loss of performance of the catalyst and so the catalyst loading was also brought down to 1 mol% Ru (Table 2.6).

**Table 2.6** Results for reactivity for the reaction of phenethyl alcohol **1.50** and amine in more solvent.



Entry <sup>[a]</sup>	Solvent	Amine	Alcohol:Amine	Amine product (%) <sup>[b]</sup>	Ester <b>2.25</b> (%) <sup>[b]</sup>
1	PhMe(2.5 mL)	<b>2.11</b>	1:1	64	3
2	PhMe (2.5 mL)	<b>2.11</b>	1:1.2	68	6
3	PhMe (2.5 mL) <sup>[c]</sup>	<b>2.11</b>	1:1.2 (dppf/Ru premix)	70	6
4	PhMe (2.5 mL)	<b>2.11</b>	1:1.5	76	3
5	DMSO(1.0 mL) <sup>[d]</sup>	<b>2.11</b>	1:1	12	0
6	PhMe (2.5 mL)	<b>2.9</b> <sup>[e]</sup>	1:1.2	0	0
7	PhMe (2.5 mL)	<b>2.13</b> <sup>[e]</sup>	1:1.2	0	0

[a] Reactions carried out on 1 mmol in toluene (2.5 mL), alcohol:amine ratio according to ratio given, 3 Å MS, 110 °C, 24 h.

[b] Conversions are based on alcohol and are determined by  $^1\text{H}$  NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

[c] The dppf/Ru premix means that the catalyst and ligand in anhydrous toluene were allowed to reflux for one hour before the substrates were added.

[d] Reactions carried out on 1 mmol in DMSO (1.0 mL), alcohol:amine ratio according to ratio given, 3 Å MS, 110 °C, 24 h.

[e] Amine **2.9** is aniline and amine **2.13** is ( $\pm$ )- $\alpha$ -methylbenzylamine.

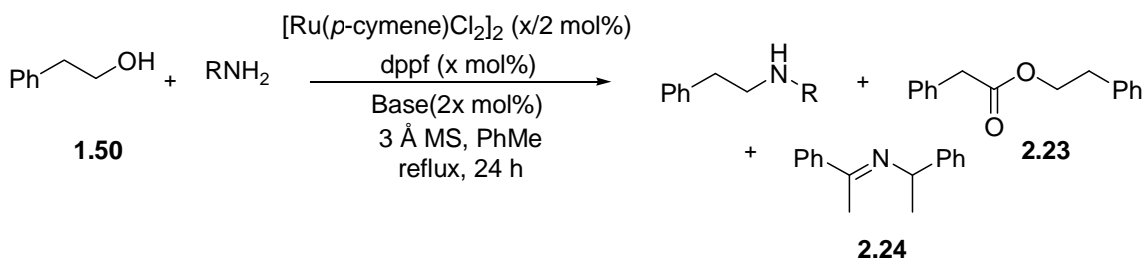
This set of screening conditions looks at conversions obtained when the catalyst loading is brought down to 1 mol% of Ru, 1 mol% of dppf, no base, no molecular sieves and 2.5 mL of solvent. We were pleased to find that the results show that the amine product can still be formed at this low catalyst loading and as the amount of starting amine is increased, the amine product increases too (Table 2.6, entries 1 to 4) *e.g.* a low catalyst loading of 1 mol% Ru is able to achieve the amine product in 76% conversion when a slight excess of amine (1.5 equivalents) is used (Table 2.6, entry 4). However, there is only a slight improvement in the amount of amine product formed by having an excess of amine during the reaction. Hence, it was decided that alcohol:amine ratio of 1:1 is best suited for this process since this would be considered more atom-efficient.

The dppf/Ru premix reaction was also carried out (Table 2.6, entry 3) and the results were almost identical to entry 2. While this screening was taking place, we were also

interested to see the effect of the use of DMSO as solvent in the catalytic system but only a low conversion of 12% of amine product was obtained (Table 2.6, entry 5). Two other reactions were performed at the time of this investigation using other amines *i.e.* aniline **2.9** and ( $\pm$ )- $\alpha$ -methylbenzylamine **2.13**. Unfortunately, at this low catalyst loading and the absence of base appear to be unsuitable for the alkylation of these less basic amines ( $pK_a$  of  $\text{PhNH}_3^+ = 4.64$ ,  $pK_a$  of  $\text{PhCHMeNH}_3^+ = 9.73$ ).

Our next strategy was to run the reaction of the alkylation of ( $\pm$ )- $\alpha$ -methylbenzylamine **2.13** with phenethyl alcohol **1.50** under similar conditions with slightly more catalyst at 0.75 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  with the addition of additives such as triethylamine, DBU, piperidinium acetate, pyridine and acetic acid at 5 mol% instead of the base, but unfortunately none of them were successful. Therefore, we reverted to varying catalyst loading for the reactions of aniline **2.9** and ( $\pm$ )- $\alpha$ -methylbenzylamine **2.13** and the results are tabulated in Table 2.7.

**Table 2.7** Results for the variation of catalyst loading for the reaction of phenethyl alcohol **1.50** and different amines.



Entry <sup>[a]</sup>	Ru loading (x mol%)	Amine	Amine Product (%)	Ester <b>2.23</b> (%) <sup>[b]</sup>	Imine <b>2.24</b> (%) <sup>[c]</sup>
1	3	<b>2.9</b>	60	0	-
2	4	<b>2.9</b>	93	7	-
3	5	<b>2.9</b>	100	0	-
4	3	<b>2.13</b>	0	0	14
5	4	<b>2.13</b>	12	0	29
6	5	<b>2.13</b>	89	0	11

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1) according to ratio given, 3 Å MS, 110 °C, 24 h.

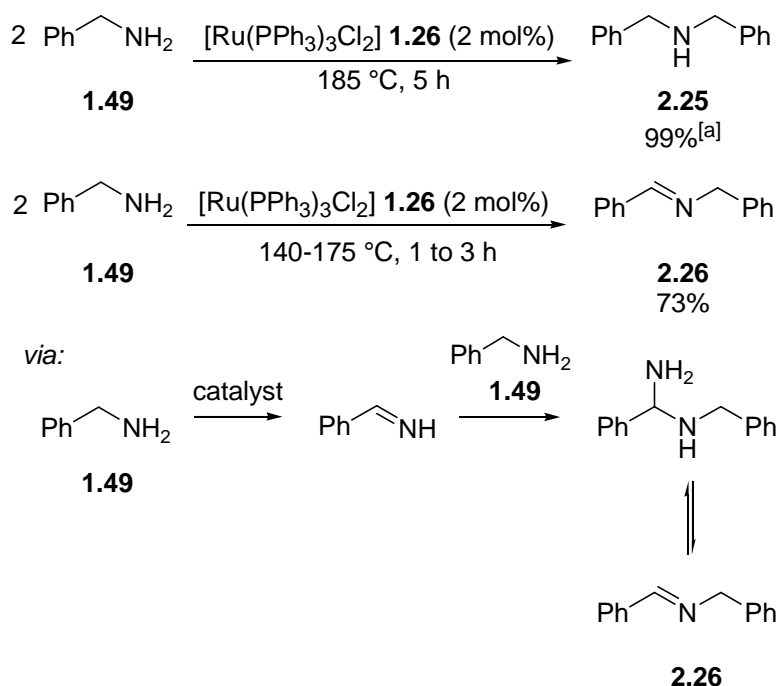
[b] Conversions are based on alcohol and are determined by  $^1\text{H}$  NMR analysis. Conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

[c] Conversions are based on amine and are determined by  $^1\text{H}$  NMR analysis. Conversion into imine (two amines) is given by the amount of amine consumed from it.

It can be seen that for the reaction of aniline **2.9** and phenethyl alcohol **1.50**, a catalyst loading of 4 mol% Ru was almost as efficient for the *N*-alkylation reaction (Table 2.7, entry 2) but a catalyst loading of 5 mol% Ru gave a full conversion into product (Table 2.7, entry 3). On the other hand, ( $\pm$ )- $\alpha$ -methylbenzylamine **2.13** required 5 mol% Ru and an imine side product was formed (Table 2.7, entry 6). The imine **2.24** is presumably formed from the self-condensation of the starting amine **2.13**. This was confirmed by the presence of a quartet at  $\delta$ 4.8 ppm which refers to the chemical shift of the benzylic proton of imine **2.24** which was consistent with the literature value.<sup>[23]</sup>

We have observed amines undergo condensation (*vide supra*) as described by Beller *et al.* (Scheme 1.38, Chapter 1)<sup>[24]</sup> and self-condensation of amines is preceded in the literature whereby ruthenium catalysts are known to catalyse the formation of symmetrical secondary amines from primary amines.<sup>[25]</sup> An example is the formation of dibenzylamine **2.25** from benzylamine **1.49** in the presence of 2 mol% of [Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub>]

(Scheme 2.11) but if the reaction is carried out for a shorter time or at a lower temperature, *n*-benzylidenebenzylamine **2.26** is formed.

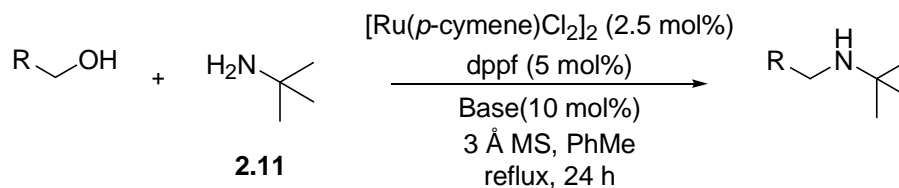


**Scheme 2.11** Formation of imine from amines in the presence of  $[\text{RuCl}_2(\text{PPh}_3)_3]$ .  
[a] Determined by GLC.

From these results, a catalyst loading of 5 mol% ruthenium (i.e. 2.5 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ ) and 5 mol% dppf was found to be optimal for the indirect alkylation of amines, otherwise side products such as esters or imines are formed.

#### 2.4.1 *N*-Alkylation of Primary Alkyl and Aromatic Amines with Benzyl Alcohol and Phenethyl Alcohol

In order to show the general applicability of this method for the alkylation of amines, a few examples of the synthesis of secondary amines were carried out using the optimised conditions and we have reported these findings recently.<sup>[26]</sup> The alkylation of *t*-butylamine **2.11** with alcohols was achieved in good yields (Table 2.8). In the case of a more hindered ortho-substituted alcohol, the reaction did not reach completion under the reaction conditions (Table 2.8, entry 2). This is an exciting result since the product has not been made before. The results of the last column (Conv. without base) will be discussed later (*vide infra*).

**Table 2.8** *N*-Alkylation of amine **2.11** with other alcohols.

Entry	Starting alcohol	Product	Conv. (%) <sup>[a][c]</sup> (with base)	Conv. (%) <sup>[b][c]</sup> (without base)
1			68 <sup>[d]</sup>	84 <sup>[d]</sup> (65)
	<b>1.52</b>	<b>2.27</b>		
2			69 <sup>[d]</sup>	87 (68)
	<b>2.28</b>	<b>2.29</b>		
3			96 <sup>[d]</sup> (88)	94
	<b>1.50</b>	<b>2.12</b>		

[a] *With base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 10 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h.

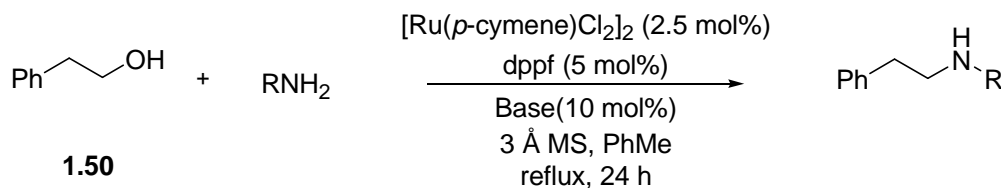
[b] *Without base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), no 3 Å MS, 110 °C, 24 h (*vide infra*).

[c] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. The values in parentheses refer to isolated yields after column chromatography.

[d] Ester formed as side product. Ester formed as a side product and conversion into ester (two alcohols) is given by the amount of alcohol consumed from it.

Other amines were also amenable to *N*-alkylation with phenethyl alcohol **1.50** (Table 2.9).

The racemic amine **2.13** was converted into product **2.14** and the use of enantiomerically pure (*R*)-**2.15** gave enantiomerically pure (*R*)-**2.16** (>97% ee), as determined from the <sup>1</sup>H NMR spectrum in the presence of (*S*)-acetylmandelic acid (Appendix A). Since a good yield was achieved for this transformation, it can be considered as a method of synthesising enantiomerically enriched amines from various alcohols as the starting substrate.

**Table 2.9** *N*-Alkylation of amines with phenethyl alcohol **1.50**.

Entry	Starting alcohol	Product	Conv. (%) <sup>[a][c]</sup> (with base)	Conv. (%) <sup>[b][c]</sup> (without base)
1 <sup>[d]</sup>	<p style="text-align: center;"><b>2.13</b></p>	<p style="text-align: center;"><b>2.14</b></p>	83 (70) <sup>[d]</sup>	100
2	<p style="text-align: center;"><b>2.15</b></p>	<p style="text-align: center;"><b>2.16</b></p>	100 (93) (>97% ee)	100
3	<p style="text-align: center;"><b>2.30</b></p>	<p style="text-align: center;"><b>2.31</b></p>	69	93 (78)

[a] *With base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 10 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h.

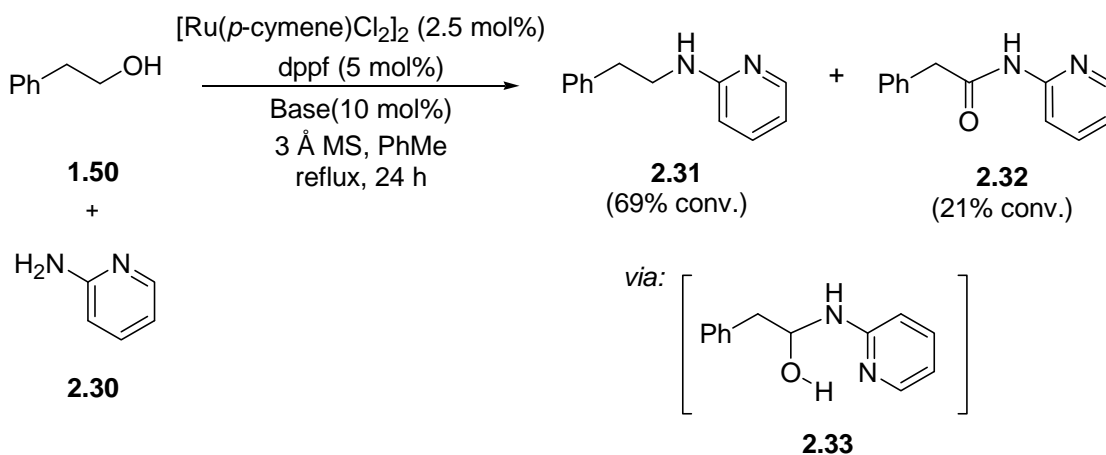
[b] *Without base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), no 3 Å MS, 110 °C, 24 h (*vide infra*).

[c] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. The values in parentheses refer to isolated yields after column chromatography.

[d] Conversion is based on amine and is determined by <sup>1</sup>H NMR analysis. Imine formed as a side product and conversion into imine (two amines) is given by the amount of amine consumed from it.

Alkylation of aminopyridine **2.30** was successful, although in this case, some amide **2.32** was found presumably due to the oxidation of the relatively stable intermediate hemi-aminal **2.33** (Scheme 2.12). This finding has been confirmed in the course of a MChem research project where MS indicated the presence of the amide product.<sup>[27]</sup>

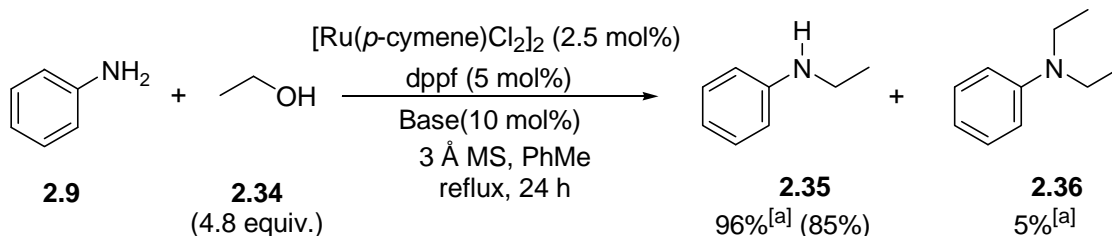




**Scheme 2.12** *N*-Alkylation of aminopyridine **2.30** with phenethyl alcohol **1.50**.

#### 2.4.2 *N*-Alkylation of Aniline with Primary Alcohols

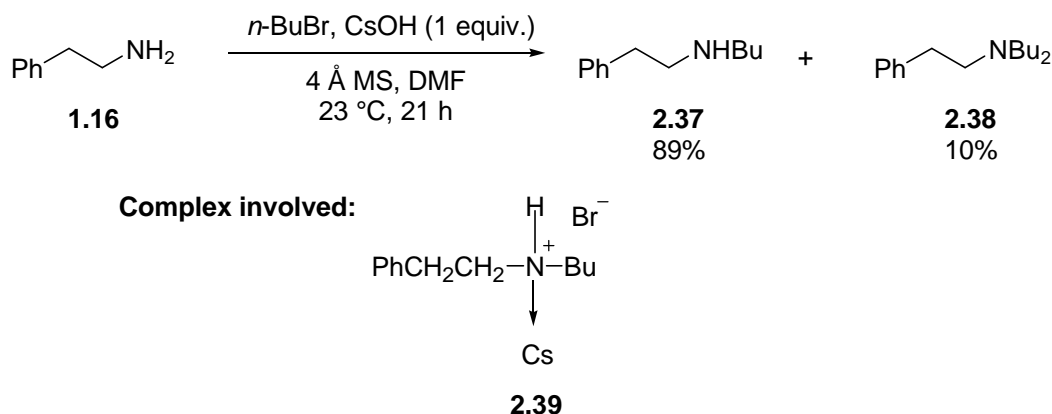
The *N*-alkylation of anilines with several alcohols was carried out. A good yield was obtained for the alkylation of aniline **2.9** with ethanol **2.34** to give *N*-ethylamine **2.35** in 95% conversion by  $^1\text{H}$  NMR analysis (85% isolated yield) and the diethylated product **2.36** was also obtained at 5% conversion (Scheme 2.13). We could not obtain a yield for this minor product because the fraction obtained for this product also had a small amount of **2.35** in it.



**Scheme 2.13** *N*-Alkylation of aniline **2.9** with ethanol **2.34**.

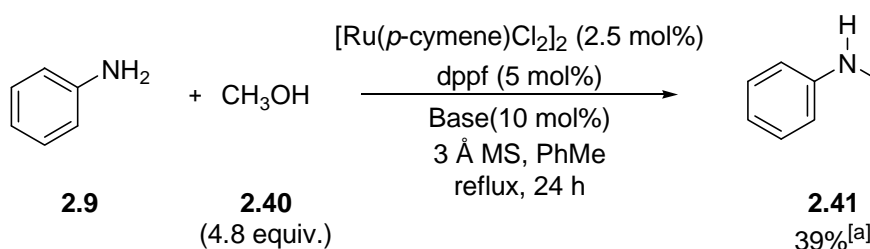
The selectivity towards the monoalkylated product is presumed to be due to the presence of base in the reaction. The effect of base in the selectivity of alkylated amine product is preceded in the literature. Salvatore *et al.* reported the ‘caesium effect’ whereby a base such as CsOH not only promoted alkylation of primary amines but also suppressed overalkylations of the produced secondary amines.<sup>[28]</sup> When phenethylamine **1.16** was coupled with a slight excess of 1-bromobutane (1.2 equiv.), a selectivity between mono- and dialkylation was obtained on the order of 9:1 (Scheme 2.14). It is believed that the dialkylamine product should coordinate strongly to the caesium ion than the corresponding amine, which would lead to the formation of the relatively stable complex **2.39**. Hence, due to the strong coordination exhibited in **2.39**, further

alkylation is suppressed by reducing the nucleophilicity of the secondary amine, therefore allowing full consumption of the primary amine **1.16**. This could also be true in the case of *N*-alkylation of aniline **2.9** with ethanol **2.34** under the “borrowing hydrogen” conditions whereby the base could be coordinating to the secondary amine product and hence making it less susceptible to further alkylation with another alcohol molecule.



**Scheme 2.14** *N*-Alkylation of phenethylamine **1.16** with using CsOH as reported by Salvatore et al. to demonstrate the ‘caesium effect’.

The *N*-alkylation of aniline **2.9** with methanol **2.40** having a lower boiling point than ethanol was also carried out (Scheme 2.15). Interestingly, this reaction is selective for the monoalkylated product but a low conversion was obtained and this could possibly be due to the fact that methanol is in a vapour form during the course of the reaction at 110 °C reflux. The reaction was repeated in excess methanol (8.6 equiv.) and unfortunately the conversion into *N*-methylaniline **2.41** only improved slightly at 41% conversion.



**Scheme 2.15** *N*-Alkylation of aniline **2.9** with with methanol **2.40** by “borrowing hydrogen”. [a] Conversion determined by <sup>1</sup>H NMR analysis.

The results obtained for the alkylation of aniline **2.9** with ethanol **2.34** is interesting because it shows that our catalyst system described here is not only restricted to phenethyl and benzyl alcohols but that aliphatic alcohols particularly ethanol can also be used as alkylating agents.

Additionally, we were also pleased to discover that the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>/dppf combination was successful for the formation of a range of *N*-phenylamines from anilines considering that the use of anilines in alkylation reactions with alcohols is usually unsuccessful (Table 2.10, entries 1-6).

**Table 2.10** *N*-Alkylation of aniline **2.9** with different alcohols.

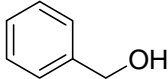
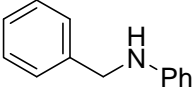
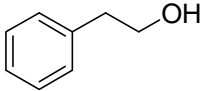
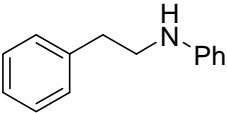
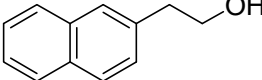
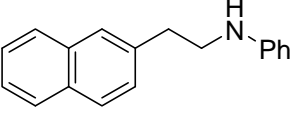
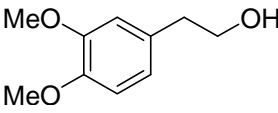
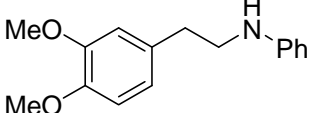
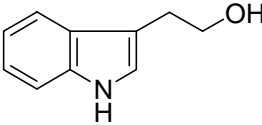
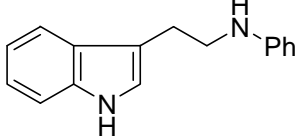
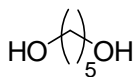
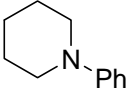
$  \begin{array}{c}  \text{R-CH}_2\text{OH} + \text{H}_2\text{N-Ph} \xrightarrow[\text{Base (10 mol\%), 3 \AA MS, PhMe, reflux, 24 h}]{\begin{array}{c} [\text{Ru}(p\text{-cymene})\text{Cl}_2]_2 \text{ (2.5 mol\%)} \\ \text{dppf (5 mol\%)} \end{array}} \text{R-CH}_2\text{N(Ph)H} \\  \text{2.9}  \end{array}  $				
Entry	Starting alcohol	Product	Conv. (%) <sup>[a][c]</sup> (with base)	Conv. (%) <sup>[b][c]</sup> (without base)
1	 <b>1.52</b>	 <b>2.42</b>	100 (80)	95
2	 <b>1.50</b>	 <b>2.10</b>	93 <sup>[d]</sup>	100 (84)
3	 <b>2.43</b>	 <b>2.44</b>	100	100(89)
4	 <b>2.45</b>	 <b>2.46</b>	100 (87)	100
5	 <b>2.47</b>	 <b>2.48</b>	100 (70)	100

Table 2.10 (continued)

Entry	Starting alcohol	Product	Conv. (%) <sup>[a][c]</sup> (with base)	Conv. (%) <sup>[b][c]</sup> (without base)
6			65 <sup>[e]</sup>	82
	<b>1.56</b>	<b>2.49</b>		

[a] *With base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 10 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h.

[b] *Without base*: Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), no 3 Å MS, 110 °C, 24 h (*vide infra*).

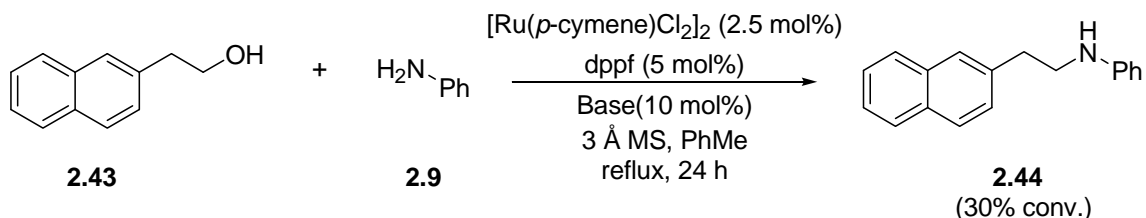
[c] Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis. Isolated yields after column chromatography. The values in parentheses refer to conversions as determined by <sup>1</sup>H NMR analysis.

[d] A small amount of ester formed as side product.

[e] Reactions conditions: 0.5 mmol in toluene (0.5 mL), alcohol:amine (2:1), 10 mol% Ru, 20 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h. Lactone formed as side product.

Entry 5 in particular is interesting since it shows that this ruthenium catalytic system can tolerate alcohol substrates bearing an indole functionality. The cyclisation of diol **1.56** with aniline **2.9** was attempted but only moderate yield was obtained. In this investigation, two equivalents of the diol were necessary to be able to get moderate yields and the catalyst loading (10 mol% Ru) was also doubled.

The results described in this sub-section show some isolated yields as well as conversions by <sup>1</sup>H NMR analysis. Recently, in the course of writing this chapter, it was decided that isolated yields should be obtained for all the compounds described in this sub-section. Using the same conditions described earlier, an attempt to rerun the *N*-alkylation of aniline **2.9** with 2-naphthylethanol **2.43** was unsuccessful (Scheme 2.16).

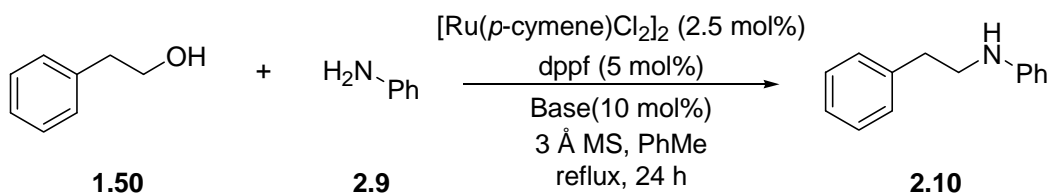


**Scheme 2.16** *N*-Alkylation of aniline **2.9** with 2-naphthylethanol **2.43**.

We were intrigued by this result and the only possible parameter that could be affecting this discrepancy is the presence of the base in the reaction. We know this since the *N*-alkylation of secondary amines does not need base in the reaction (see Chapter 3 and

Chapter 4). We chose the alkylation of aniline **2.9** with phenethyl alcohol **1.50** as a model reaction.

**Table 2.11** Results for the *N*-alkylation of aniline **2.9** with phenethyl alcohol **1.50** under different conditions.



Entry	Base (10 mol%)	3 Å MS	Conversion <sup>[a]</sup> (%)
1	K <sub>2</sub> CO <sub>3</sub>	0.52 g	50
2	K <sub>2</sub> CO <sub>3</sub>	0.52 g	33
3 <sup>[b]</sup>	No base	0.52 g	93
4 <sup>[c]</sup>	No base	-	100

[a] Reactions carried on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 10 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h. Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis.

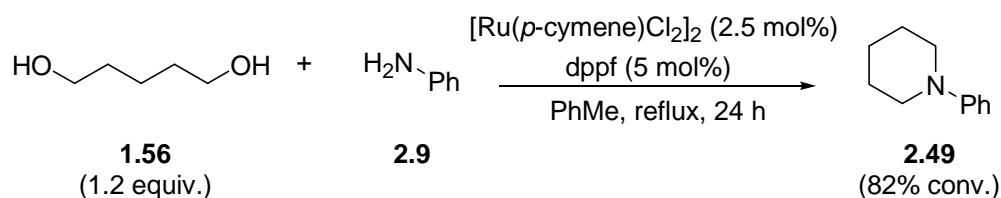
[b] Reactions carried out without base.

[c] Reactions carried out without base and without 3 Å MS.

Entry 1 in Table 2.11 shows that in the presence of base, a conversion of 50% to product was obtained. Entry 2 is an identical reaction but it is carried out in a Radley's carousel tube (Radley's tubes have been used in all the screenings as described before) and an even lower conversion was obtained. When the reactions were carried out without base, excellent conversions were obtained (Table 2.11, entries 3 and 4). The only difference between entries 3 and 4 is that entry 4 was carried out without the use of 3 Å MS. Hence, the results show that the role of base affects the results considerably. It is also worth pointing out that we have used a new reagent bottle for aniline. Therefore, the aniline used previously in the screenings could possibly be contaminated although previously it was distilled before use.

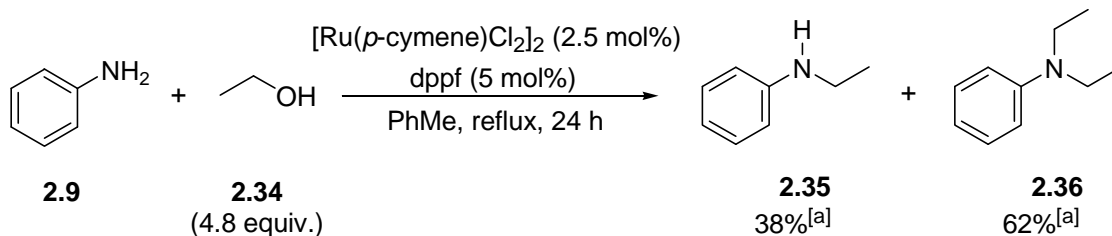
Hence, all the reactions done in the presence of base previously were repeated without base and 3 Å MS and good to excellent conversions were obtained and isolated yields

were obtained for the products that were not isolated before (Tables 2.8-2.10). It is also worth noting that all these reactions without base were carried out in Young's tap carousel tubes. There are three accomplishments obtained from this set of results without base. Firstly, aminopyridine **2.30** was successfully alkylated with phenethyl alcohol by using  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}$  combination without base at 78% isolated yield (100% conversion). No side products were formed during the reaction and this implies that the presence of base favoured the formation of amide **2.32** (refer Table 2.9). Secondly, an improved synthesis of cyclic product **2.49** was achieved. Andrew Watson from our group, very recently, has fully optimised the *N*-alkylation of anilines with different diols.<sup>[29]</sup> With his optimised conditions, the cyclisation reaction was rerun (Table 2.10, entry 6) but using dppf instead of DPEphos as the ligand and a good conversion was obtained for the reaction (Scheme 2.17).



**Scheme 2.17** *N*-Alkylation of aniline **2.9** with 1,5-pentanediol **1.56**.

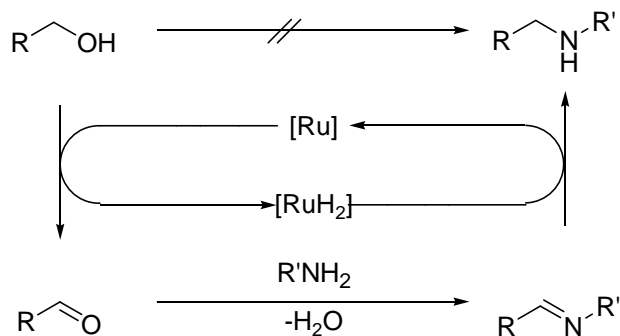
Thirdly, the *N*-alkylation of phenethyl alcohol with ethanol was also carried out using  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}$  combination without base at the same conditions depicted in Scheme 2.13. We were surprised to discover that it had an opposite effect on the selectivity of the alkylated product (Scheme 2.18) as compared to what has been described earlier (Scheme 2.13). We reasoned that in the absence of base, no “caesium effect”<sup>[28]</sup> is taking place and hence both mono and dialkylated amine products are obtained (*vide supra*).



**Scheme 2.18** *N*-Alkylation of aniline **2.9** with simple alcohols. <sup>[a]</sup> Conversion determined by <sup>1</sup>H NMR analysis.

The Ru/dppf catalytic system is a comparable system to the one done by Yamaguchi *et al.*<sup>[14]</sup> and could be considered an economical method for the *N*-alkylation of amines that requires the use of less expensive commercially available ruthenium catalyst/ligand

than the ones reported in the literature. The reaction is thought to proceed *via* the “borrowing hydrogen” concept which had been reported by the Williams group.<sup>[5]</sup> As shown in Scheme 2.19, hydrogen is temporarily taken away from the alcohol to give an intermediate aldehyde, which undergoes imination with an amine added to the reaction to afford an imine. The hydrogen is then returned by the catalyst thus reducing the imine to an amine.



**Scheme 2.19** Indirect N-alkylation of amines proposed for the Ru/dppf catalyst.

## 2.5 Chapter Summary

The  $[Ir(COD)Cl]_2/dppf/K_2CO_3$  conditions were found to be highly efficient for the N-alkylation of benzylamine with phenethyl alcohol by “borrowing hydrogen” but is only moderately efficient for other amines such as *t*-butylamine and methylbenzylamine. The search for a ruthenium catalyst that would do the amination chemistry efficiently was carried out and it was discovered that the  $[Ru(p\text{-cymene})Cl_2]_2/dppf/K_2CO_3$  combination was best suited for this transformation *via* “borrowing hydrogen” and optimisation of the reaction was also carried out. The results of this study have been published.<sup>[26]</sup> Subsequently, it was discovered that the addition of additives such as molecular sieves and base had no obvious beneficial effect on these reactions and were therefore omitted in our recent investigation (‘Without base’ column in Tables 2.8-2.10). Hence, a number of primary alcohols and primary amines were converted into the corresponding secondary amines in good to excellent yields by simply heating a solution of the alcohol and amine at reflux in toluene in the presence of 2.5 mol% of  $[Ru(p\text{-cymene})Cl_2]_2$  and 5 mol% dppf for 24 hours. Also at the time of the discovery of this ruthenium system, Beller *et al.* reported the N-alkylation of amines with alcohols using  $[Ru_3(CO)_{12}]/N\text{-phenyl-2-(dicyclohexylphosphanyl)pyrrole}$  (*vide supra*, Scheme 1.36, Chapter 1).<sup>[30]</sup>

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## Chapter 3

### 3. Results and Discussion II

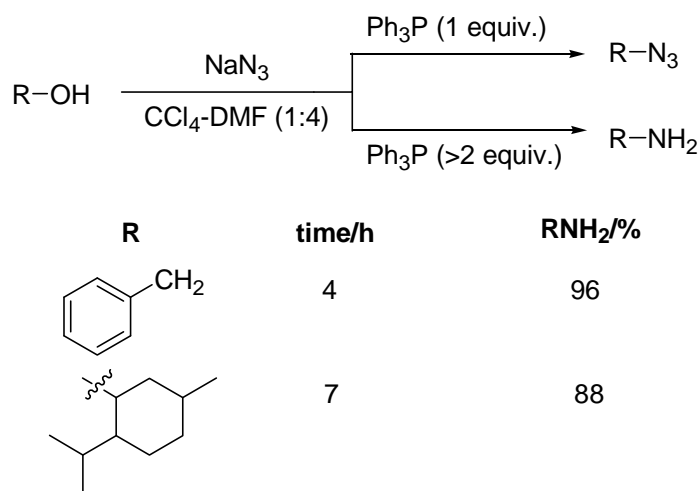
The synthesis of secondary and tertiary amines has been achieved by the ruthenium-catalysed *N*-alkylation of amines with alcohols by “borrowing hydrogen”.

#### 3.1 Aim

To apply the “borrowing hydrogen” strategy in the synthesis of primary, secondary and tertiary amines.

#### 3.2 Background

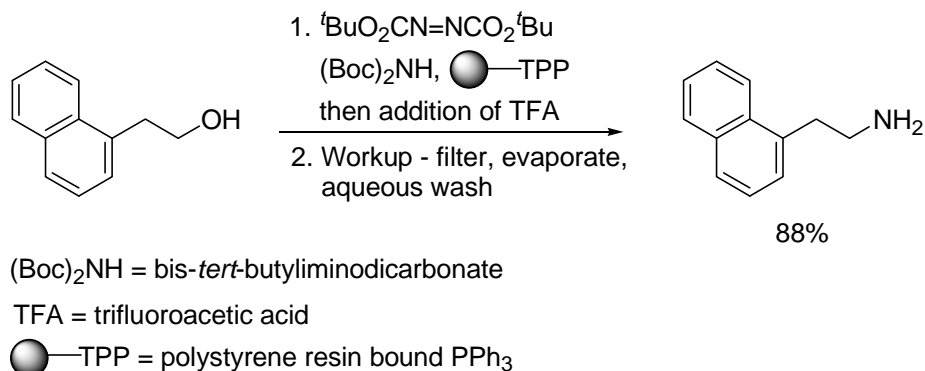
The transformation of alcohols to amines is an important reaction for the synthesis of a variety of organic compounds.<sup>[1]</sup> The most common procedure involves a three-step strategy: a) conversion of alcohols into corresponding halides or sulfonates, b) nucleophilic substitution by azide anion<sup>[2]</sup> and c) reduction of azide to amine by using various reagents.<sup>[3]</sup> Another common procedure involves a Mitsunobu reaction followed by the Staudinger reaction which finally affords the amine product.<sup>[4]</sup> There are only a few methods precedent in the literature that describe this functional group manipulation in a single operation.<sup>[1], [4-5]</sup> An example is shown in Scheme 3.1 that describes a one-pot protocol for the conversion of alcohols into azides/amines using  $\text{NaN}_3$  and  $\text{PPh}_3$  in  $\text{CCl}_4$ -DMF (1:4).<sup>[1]</sup>



**Scheme 3.1** Conversion of alcohols into azides/amines.

The formation of amines occurs as the initial azide formed reacts with the second equivalent of  $\text{PPh}_3$  giving the iminophosphorane which in turn is converted into the amine upon treatment with water. Treatment of alcohols with one molar equivalent of  $\text{PPh}_3$  gave azides exclusively in good yield confirming the azide as the intermediate.

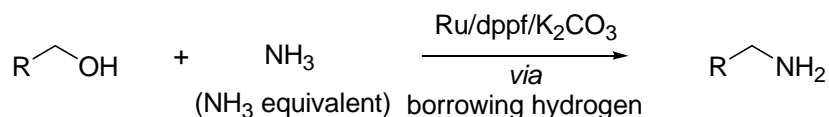
The only recent one-pot strategy for the transformation of primary alcohols to primary amines is described by Sun and Pelletier *via* a modified Mitsunobu reaction protocol.<sup>[6]</sup> As shown in Scheme 3.2, the reaction involves the use of polystyrene resin bound  $\text{PPh}_3$  (4.0 equiv.) in the presence of bis-*tert*-butyliminodicarboxylate (4.0 equiv.) followed by treatment with di-*tert*-butylazodicarbonate (3.0 equiv.). The treatment with TFA would then cleave the protected amine product and a typical aqueous workup would lead to the final amine product.



**Scheme 3.2** Conversion of primary alcohol into primary amine.

This procedure is suitable for parallel synthesis but the use of excess reagents and the thermal hazards associated with azodicarboxylates are obviously not practical for large scale preparations.<sup>[7]</sup> This takes us back to our main focus in the direct transformation of primary alcohols and ammonia to primary amines. Although there are patents that describe the continuous production of primary amines, they usually involve reductive amination between a primary alcohol with ammonia and hydrogen. The reaction has been used for a variety of R groups ranging from methyl ( $\text{C}_1$ ) to primary alkyl groups in the hexadecyl ( $\text{C}_{16}$ ) detergent range.<sup>[8]</sup> Heterogeneous catalysts are frequently used which contain either metals or metal oxides such as copper chromite<sup>[9]</sup> impregnated into silica, alumina, or similar supports that are used as a dehydrogenation catalyst and this usually is conducted at a temperature from 240 to 320 °C.<sup>[10]</sup>

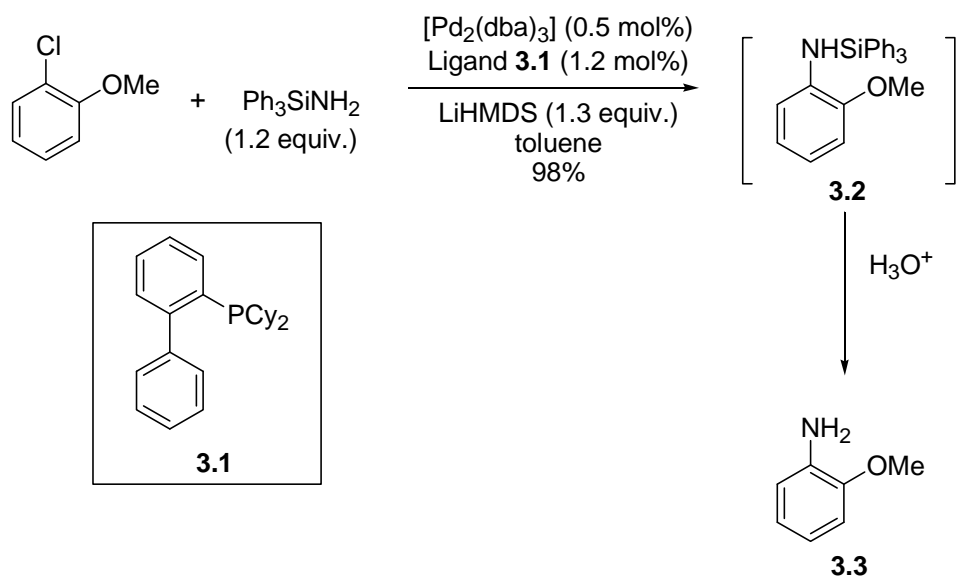
The conversion of primary alcohols into primary amines is a highly desirable process if the transformation could be achieved in one step. Our interest in the direct transformation of primary alcohol to primary amine prompted us to examine the possibility of the synthesis of primary amines by the “borrowing hydrogen” strategy and this would certainly complement the existing ruthenium-catalysed *N*-alkylation of primary amines with primary alcohols described in Chapter 2. One possibility to achieve this is the utilisation of ammonia or its simple salts as nitrogen sources by the “borrowing hydrogen” methodology (Scheme 3.3).



**Scheme 3.3** *Proposed direct amination of alcohols.*

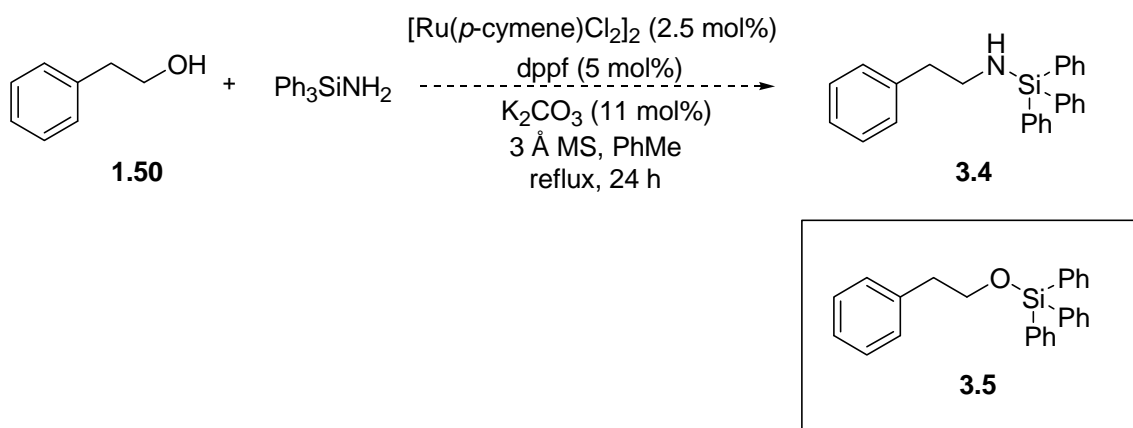
### 3.3 Initial Studies

In order to achieve this transformation, the use of ammonia itself or simple salts as an ammonia equivalent would be required in the reaction. A review on the use of ammonia in catalytic reactions has been described by Roundhill in 1992.<sup>[10]</sup> There have been some reports recently<sup>[11]</sup> on the use of ammonia or ammonia equivalents in homogeneous catalytic systems as substrate. Among these reactions include palladium-catalysed telomerisation of butadiene and ammonia giving primary alkylamines,<sup>[12]</sup> rhodium- and iridium-catalysed reductive amination of carbonyl compounds with ammonium formate and ammonia affording primary alkylamines,<sup>[13]</sup> and copper- and palladium-catalysed coupling reaction of ammonia with aryl halides producing arylamines.<sup>[14-15]</sup> An earlier example by Buchwald has described the use of inexpensive LiN(SiMe<sub>3</sub>)<sub>2</sub> (LiHMDS), aminotriphenylsilane (Ph<sub>3</sub>SiNH<sub>2</sub>) and LiNH<sub>2</sub> as ammonia equivalents for the Pd-catalysed coupling of aryl halides in the presence of Buchwald ligand **3.1**.<sup>[16]</sup> An example is shown in Scheme 3.4 where Ph<sub>3</sub>SiNH<sub>2</sub> can be used as an ammonia surrogate and the coupled product of **3.2** was easily deprotected to give **3.3**.



**Scheme 3.4** Buchwald's amination of hindered aryl halide with  $\text{Ph}_3\text{SiNH}_2$ .

As a starting point of our investigation, we examined the reaction of  $\text{Ph}_3\text{SiNH}_2$  as our ammonia equivalent in the ruthenium-catalysed *N*-alkylation of ammonia with phenethyl alcohol by “borrowing hydrogen”. It was proposed that after performing the reaction with an alcohol under the  $\text{Ru}/\text{dppf}/\text{K}_2\text{CO}_3$  conditions, the  $\text{Ph}_3\text{Si}$  group can then be cleaved with acid and this approach would potentially lead to the transformation of the hydroxyl group to an amine group. Phenethyl alcohol is chosen as our model reaction and is subjected to the conditions for “borrowing hydrogen” as described in Chapter 2 (Scheme 3.5).

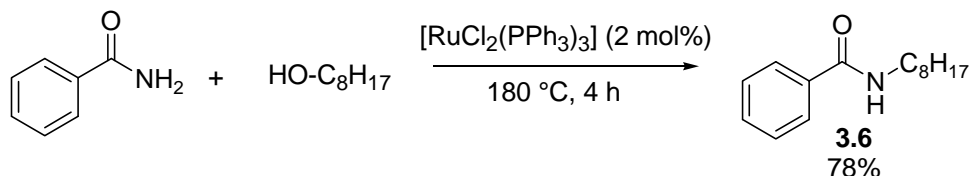


**Scheme 3.5** Attempted *N*-alkylation of  $\text{Ph}_3\text{SiNH}_2$  as ammonia equivalent via “borrowing hydrogen”.

Unfortunately, the analysis of the crude reaction mixture by MS indicated that none of the desired silylated amine product **3.4** was obtained. Instead, the product obtained

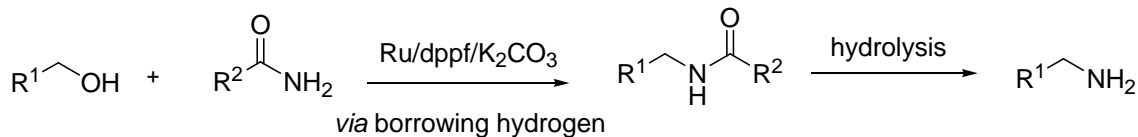
mostly in the crude mixture was the silylated alcohol product **3.5** and this is presumably due to the fact that silicon has a high affinity for oxygen atoms.

The *N*-alkylation of amides on treatment with alcohols and a ruthenium complex has precedent in the literature.<sup>[17]</sup> An example is shown in Scheme 3.6 whereby benzamide has been converted into the secondary amide **3.6**. It is worth noting that these experiments were carried out at a high temperature of 180 °C.



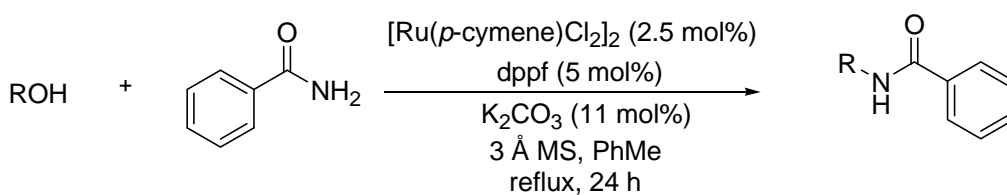
**Scheme 3.6** Direct amination of alcohol via amide as the ammonia surrogate strategy.

We then proposed to consider the use of an amide as a simpler ammonia surrogate in the “borrowing hydrogen” using the Ru/dppf/K<sub>2</sub>CO<sub>3</sub> conditions and again the amide group can then be cleaved with acid and this approach would potentially lead to the direct transformation of the hydroxyl group to an amine group (Scheme 3.7).



**Scheme 3.7** Direct amination of alcohol via amide as the ammonia surrogate strategy.

The results of several attempts using benzamide as the ammonia surrogate by the “borrowing hydrogen” strategy are listed Table 3.1. Treatment of equimolar amounts of benzamide with phenethyl alcohol under the Ru/dppf/K<sub>2</sub>CO<sub>3</sub> conditions only gave a low conversion of 16% (Table 3.1, entry 1). Among the other alcohols examined under the same conditions but in excess of the alcohol are ethanol, methanol and propanol but none of them had any improvement on the conversion (Table 3.1, entries 2-6). Since the reported procedure (Scheme 3.6) had been carried out at a high temperature of 180 °C, the reaction between benzamide with ethanol were carried out under the Ru/dppf/K<sub>2</sub>CO<sub>3</sub> conditions at a higher temperature of 135 °C using xylene as the solvent, but the amination did not occur at all (Table 3.1, entry 7). From these results, we reasoned that the amide is an unsuitable alkylating reagent in the *N*-alkylation reaction by “borrowing hydrogen” and this is presumably due to the low basicity of amides as well as its low ability to act as a nucleophile in the reaction.

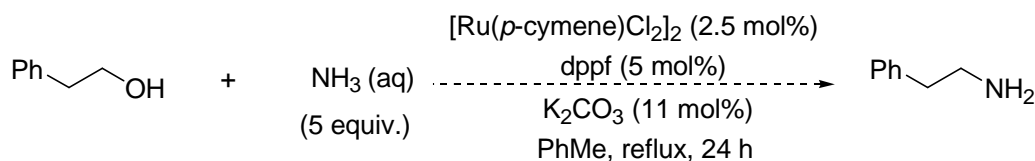
**Table 3.1** Attempted *N*-alkylation of amides by “borrowing hydrogen”.

Entry	R (no. of equivalents)	Conversion <sup>[a]</sup> (%)
1	PhCH <sub>2</sub> (1 equiv.)	15
2	CH <sub>3</sub> CH <sub>2</sub> (4 equiv.)	8
3	CH <sub>3</sub> CH <sub>2</sub> (8 equiv.)	trace
4	CH <sub>3</sub> (8 equiv.)	trace
5	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> (4 equiv.)	5
6	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> (8 equiv.)	6
7 <sup>[b]</sup>	CH <sub>3</sub> CH <sub>2</sub> (4 equiv.)	0

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 10 mol%  $\text{K}_2\text{CO}_3$ , 110 °C, 24 h. Conversions are based on alcohol and are determined by  $^1\text{H}$  NMR analysis.

[b] Reaction carried out in xylene.

Our next strategy is to use ammonia itself but due to safety concerns and scale-up issues<sup>[18]</sup> related with ammonia, we proposed to use aqueous  $\text{NH}_3$ . An attempt in using aqueous ammonia as the alkylating reagent was carried out but the amination did not occur at all (Scheme 3.8).

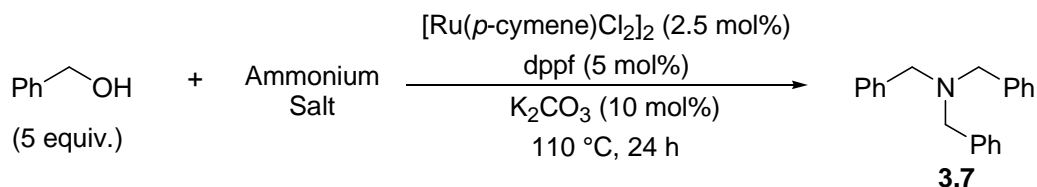
**Scheme 3.8** Direct amination of alcohol using aqueous ammonia by “borrowing hydrogen”.

From this reaction, we only recovered starting material from the crude reaction mixture and we reasoned that the water from aqueous  $\text{NH}_3$  could have deactivated the catalyst.

We then continued our investigations with ammonium salts as they are more easily and safely handled than ammonia itself (Table 3.2). The conditions for these reactions were

carried out under the Ru/dppf/K<sub>2</sub>CO<sub>3</sub> conditions at 110 °C without solvent but the alcohol is used in vast excess (5 equiv.). This is to ensure there is a greater chance for the ammonia molecule to react with an alcohol molecule in the reaction.

**Table 3.2** *N*-Alkylation of ammonium salts by “borrowing hydrogen”.



Entry	Ammonium salt	Conversion <sup>[a]</sup> (%)
1	NH <sub>4</sub> CH <sub>3</sub> CO <sub>2</sub>	68 <sup>[b]</sup>
2	NH <sub>4</sub> HCO <sub>2</sub>	0
3	NH <sub>4</sub> Cl	2
4	NH <sub>4</sub> Br	6
5	NH <sub>4</sub> SO <sub>4</sub>	3
6	(NH <sub>4</sub> ) <sub>4</sub> C <sub>2</sub> O <sub>4</sub> ·H <sub>2</sub> O	0
7 <sup>[b]</sup>	NH <sub>4</sub> BF <sub>4</sub>	5

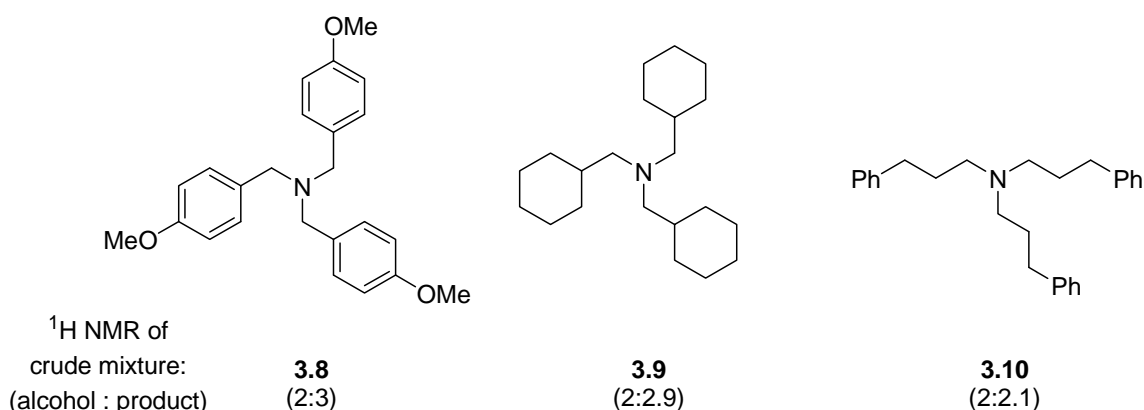
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:ammonium salt (5:1), 3 Å MS, 10 mol% K<sub>2</sub>CO<sub>3</sub>, 110 °C, 24 h. Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis.

[b] This refers to isolated yield.

When the reaction of ammonium acetate with benzyl alcohol (5 equiv.) in the presence of 2.5 mol% of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>) and 5 mol% dppf was carried out at 110 °C without solvent, tribenzylamine **3.7** was obtained in 68% yield (Table 3.2, entry 1). This seems to imply that the alcohol did undergo amination under these conditions (as we proposed) but the amine product reacted further with another aldehyde followed by reduction to form a secondary amine and then went on another similar step to give a tertiary amine as the final product. This suggests that the catalytic reaction had undergone triple *N*-alkylation that involves dehydrogenation, imine or iminium ion formation, and hydrogenation. The results of the reactions of other ammonium salts such as ammonium formate and ammonium halides are summarised in Table 3.2 (entries 2 to 7) but unfortunately only starting material was recovered in most cases.



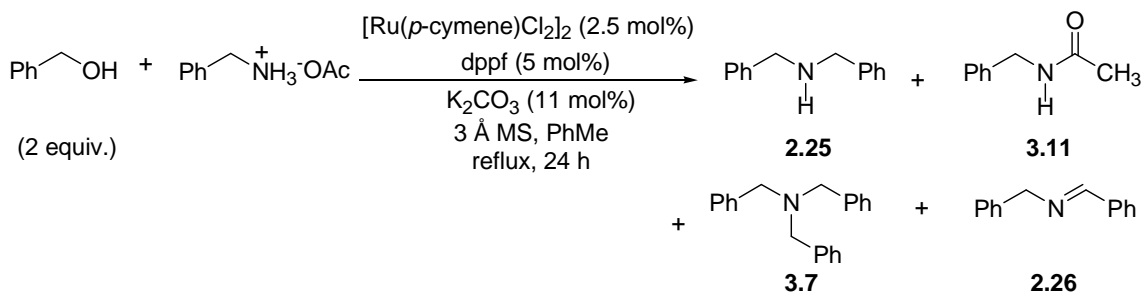
We carried on the investigation with the trialkylation reactions of ammonium acetate with three other primary alcohols (Figure 3.1) under the same conditions described in Table 3.2 and we were pleased to find that all three alcohols gave the trialkylated amine product but conversions were difficult to interpret due to the overlapping of the alkyl groups of the starting material and the product in the same region in the  $^1\text{H}$  NMR spectrum. Therefore, the starting alcohol to amine product ratio (alcohol:product) obtained by comparison of the integral peaks from  $^1\text{H}$  NMR analysis are only given then (Figure 3.1).



**Figure 3.1** Trialkylated amine products obtained from the reaction between ammonium acetate and three other alcohols by “borrowing hydrogen”.

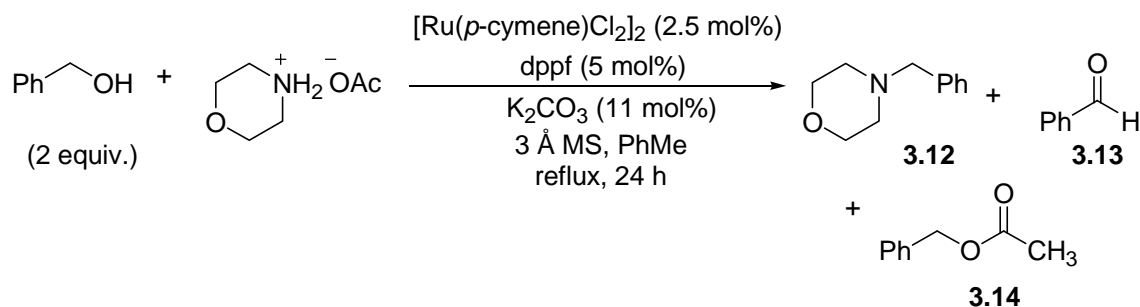
While this finding is novel, we did not pursue any further investigation of this trialkylation reaction with ammonium acetate. At the time we reported this finding, Yamaguchi *et al.* also reported the selective synthesis of tertiary amines by  $\text{Cp}^*\text{IrCl}_2$  catalysed multialkylation of ammonium salts with alcohols and this methodology has been described in Chapter 1 (Scheme 1.46).

We speculated whether the acetate had an effect on the trialkylation reaction and benzyl ammonium acetate was used instead to see if we would get a better conversion into the tertiary amine. Two reactions were carried out with benzyl alcohol (2 equiv.) and benzyl ammonium acetate (1 equiv.) in the presence of 2.5 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  and 5 mol% dppf at 110  $^\circ\text{C}$  with 1 mL of toluene. The first experiment is shown in Scheme 3.9.



**Scheme 3.9** Benzylation of benzyl ammonium acetate by “borrowing hydrogen”.

We proposed that by using two equivalents of alcohol in the reaction would proceed directly to the tertiary amine product, but as shown in Scheme 3.10, a mixture of products was obtained instead. The exact conversions of the side products were difficult to analyse but mostly starting material was obtained followed by the methyl benzamide **3.11**, dibenzylamine **2.25**, imine **2.26** and the tribenzylamine product **3.7** was the least. A similar experiment was also conducted at the same time but without using base and the crude mixture showed some recovered starting alcohol, a small amount of benzamide and tribenzylamine was the major product. This shows that the presence of base favoured the formation of imine and dialkylated amine. This investigation with benzylammonium acetate is not very selective towards the formation of tertiary amine and an investigation with morpholine acetate was carried out (Table 3.3). Morpholine is a secondary amine and we speculated that a tertiary amine should only be formed as the product in a reaction with benzyl alcohol (imine and secondary amine as side product is thus avoided) under the “borrowing hydrogen” conditions.

**Table 3.3** *N*-Alkylation of morpholine acetate with benzyl alcohol by “borrowing hydrogen”.

Entry	Conditions	Conversion <sup>[a]</sup> (%)		
		3.12	3.13	3.14
1	Base, solvent	100	14	0
2	No base, solvent	90	11	19
3 <sup>[b]</sup>	No base, no solvent	79	18	4

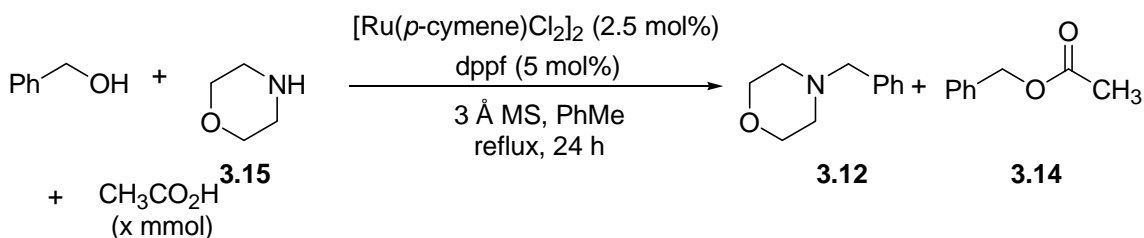
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:ammonium salt (2:1), 3 Å MS, 10 mol%  $\text{K}_2\text{CO}_3$ , 110 °C, 24 h. Conversions are based on alcohol (where 100% equates to complete conversion of morpholinium acetate) and are determined by  $^1\text{H}$  NMR analysis.

We were pleased to find that morpholine is benzylated successfully under the normal “borrowing hydrogen” conditions (Table 3.3, entry 1). However, when the reaction was carried out without base, a good conversion was obtained but benzaldehyde and acetyl benzylate are formed as side products (Table 3.3, Entry 2). When the reaction was carried out neat without the base, the conversion into the product decreased and benzaldehyde was formed mostly as the side product (Table 3.3, Entry 3). We reasoned that the side products could be avoided by running the reactions at equivalent amounts of alcohol:amine (1:1). Also, at this point, the results showed that the alkylation reaction could proceed without base (Table 3.3, entry 2) and we next investigated whether it was necessary to preform the acetate by injecting the right amount of morpholine and glacial acetic acid instead at the start of the reaction (Table 3.4).

When the reactions were carried out with morpholine **3.15** and glacial acetic acid, complete conversion into the product was obtained (Table 3.4, entries 1, 4, 5) and the amount of glacial acetic acid does not affect it. Entry 2 (Table 3.4) is similar to the reaction for Entry 2 (Table 3.3) but glacial acetic acid and morpholine **3.15** were used instead of preforming the morpholine acetate at the start of the reaction and complete conversion into the product was also obtained. We were intrigued by the results obtained when the reaction was performed without the presence of glacial acetic acid

(Table 3.4, entry 4). This implies that morpholine **3.15** is benzylated under the “borrowing hydrogen” conditions without the need of an additive such as acetate ions. In other words, secondary amines can be alkylated with the same conditions for primary amines as reported in Chapter 1 without the need of base in the reaction. This is an important finding as at the time that this investigation was carried out, the *N*-alkylation of secondary amines with primary alcohols as the alkylating reagent using a ruthenium catalyst has not been reported before. Entries 5 and 6 (Table 3.4) shows the importance of the use of ligand in the reaction.

**Table 3.4** *N*-Alkylation of morpholine with benzyl alcohol in the presence of glacial acetic acid by “borrowing hydrogen”.



Entry	AcOH (mmol)	Conversion <sup>[a]</sup> (%)	
		<b>3.12</b>	<b>3.14</b>
1	1 mmol	100	trace
2 <sup>[b]</sup>	1 mmol	100	14
3	No acid	100	0
4	0.2 mmol	100	0
5	0.5 mmol	100	0
5 <sup>[c]</sup>	1.0 mmol	0	trace
6 <sup>[c], [d]</sup>	-	0	trace

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:morpholine (1:1), 3 Å MS, 110°C, 24 h. Conversions are based on alcohol and are determined by <sup>1</sup>H NMR analysis.

[b] 2 mmol of alcohol was used.

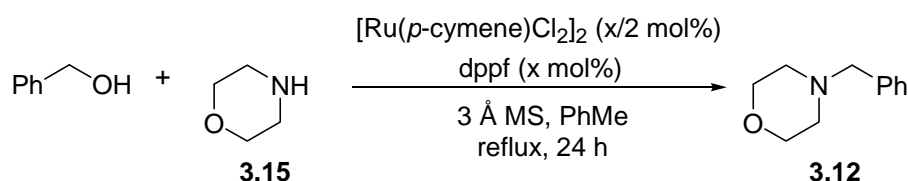
[c] Reaction was carried out without ligand.

[d] Morpholine acetate was used instead of morpholine and glacial acetic acid.

Hence, our next strategy was to optimise further the catalytic conditions by lowering its catalyst loading (Table 3.5). In comparison with the results of our reported investigation for primary amines where 5 mol% ruthenium catalyst had been employed

(Chapter 2), it could be shown that a catalyst loading of 2.5 mol% is sufficient to obtain excellent yields (Table 3.5, entry 3). However, a low catalyst of 1 mol% Ru proved to be unsuitable for the alkylation reaction since starting material was mostly recovered as well as other unknown side products (Table 3.5, entry 4). Finally, a catalyst concentration of 1.25 mol%  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  and 2.5 mol% dppf was found to be optimal.

**Table 3.5** Optimisation of the *N*-alkylation of morpholine with benzyl alcohol by “borrowing hydrogen”.



Entry	Ru loading (x mol%)	Conversion <sup>[a]</sup> (%)
1	5.0	100
2	4.0	100
3	2.5	100
4 <sup>[b]</sup>	1.0	Low conversion with unknown side products


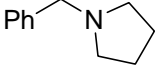
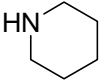
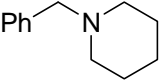
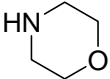
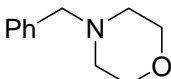
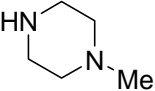
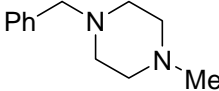
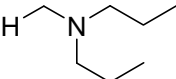
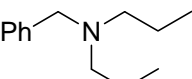
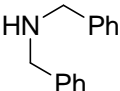
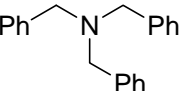
[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:morpholine (1:1), 3 Å MS, 110 °C, 24 h. Conversions are based on alcohol and are determined by  $^1\text{H}$  NMR analysis.

[b] Starting material mostly recovered.

### 3.4 Ruthenium-Catalysed *N*-Alkylation of Primary Alcohols with Secondary Amines by Borrowing Hydrogen

In order to show the general applicability of this improved ruthenium-catalysed *N*-alkylation reaction by “borrowing hydrogen”, various secondary amines were alkylated using 1.25 mol%  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (2.5 mol% of Ru) with 2.5 mol% dppf as the diphosphine ligand. The products were isolated and purified by column chromatography in good yields (Table 3.6). The reactions were successful for the alkylation of both cyclic (Table 3.6, entries 1-4) and acyclic (Table 3.6, entries 5) amines with the exception of dibenzylamine (Table 3.6, entry 6). A low conversion of 51% was only obtained, leading to a lower isolated yield and this is possibly due to the amine coordinating to the catalyst as a ligand in the reaction.

**Table 3.6** Benzylation of secondary amines.

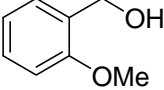
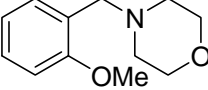
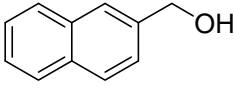
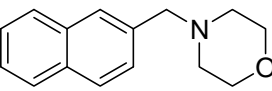
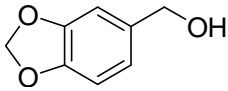
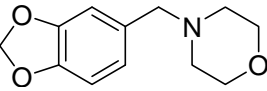
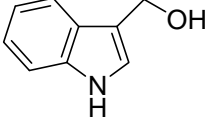
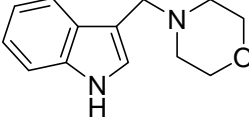
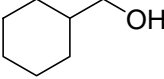
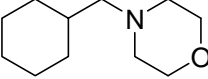
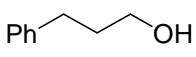
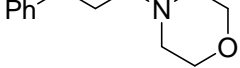
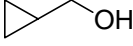
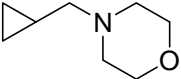
$\text{Ph-CH}_2\text{-OH} + \text{R}_2\text{NH} \xrightarrow[\substack{3 \text{ \AA MS, PhMe} \\ \text{reflux, 24 h}}]{\substack{[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2 (1.25 \text{ mol\%}) \\ \text{dppf} (2.5 \text{ mol\%})}} \text{Ph-CH}_2\text{-NR}_2$			
Entry	Starting alcohol	Product	Isolated Yield (%) <sup>[a]</sup>
1	 <b>3.16</b>	 <b>3.17</b>	71
2	 <b>3.18</b>	 <b>3.19</b>	72
3	 <b>3.15</b>	 <b>3.12</b>	84
4	 <b>3.20</b>	 <b>3.21</b>	80
5	 <b>3.22</b>	 <b>3.23</b>	87
6	 <b>2.25</b>	 <b>3.7</b>	44

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

Having shown that several amines could be successfully used in the amination of benzyl alcohol, we wished to explore the range of alcohols that could be used. We chose to examine the alkylation of morpholine with a range of alcohols (Table 3.7). We were pleased to find that benzylic alcohols (Table 3.7, entries 1-5) were all cleanly alkylated under these conditions. All of these reactions, including the formation of an ortho-substituted benzylamine (Table 3.7, entry 2) proceeded essentially to completion, the variation in yield simply being a consequence of the relative ease of isolation. The aliphatic amines (Table 3.7, entries 7 and 8) were also formed with 100% conversion,

although the branched product (Table 3.7, entry 6) only proceeded to 75% conversion under these reaction conditions, leading to a lower isolated yield.

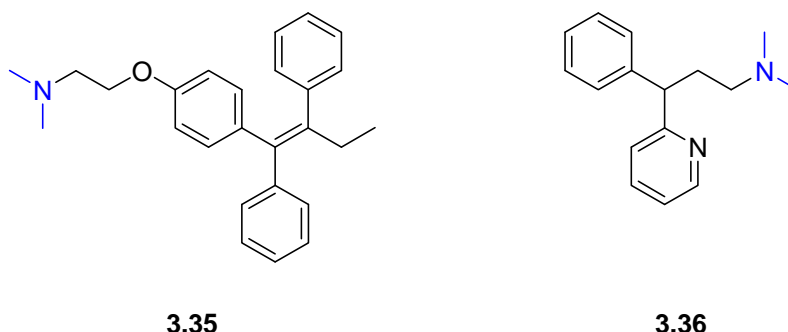
**Table 3.7** *N*-Alkylation of morpholine with different primary alcohols.

$\text{R-OH} + \text{Morpholine} \xrightarrow[\substack{3 \text{ \AA MS, PhMe} \\ \text{reflux, 24 h}}]{\substack{[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2 (1.25 \text{ mol\%}) \\ \text{dppf} (2.5 \text{ mol\%})}} \text{R-Morpholine}$			
Entry	Starting alcohol	Product	Isolated yield (%) <sup>[a]</sup>
1	Ph-CH <sub>2</sub> -OH	Ph-CH <sub>2</sub> -N-morpholine	84
2	<div> <div>1.52</div>  <div>2.28</div> </div>	<div> <div>3.12</div>  <div>3.24</div> </div>	74
3	<div> <div>2.43</div>  </div>	<div> <div>3.25</div>  </div>	78
4	<div> <div>3.26</div>  <div>2.47</div> </div>	<div> <div>3.27</div>  <div>3.28</div> </div>	89
5	<div> <div>3.26</div>  <div>2.47</div> </div>	<div> <div>3.27</div>  <div>3.28</div> </div>	85
6	<div> <div>3.29</div>  </div>	<div> <div>3.30</div>  </div>	62
7	<div> <div>3.31</div>  </div>	<div> <div>3.32</div>  </div>	77
6	<div> <div>3.33</div>  </div>	<div> <div>3.34</div>  </div>	85

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:amine (1:1), 3 Å MS, 110 °C, 24 h.

### 3.5 Ruthenium-Catalysed Synthesis of Dimethylamines by Borrowing Hydrogen

Dimethylamino analogues are an important class of compounds due to the common occurrence of the dimethylamino group in many biologically active compounds. Effexor, Antergan and Tripeleminamine are some examples of medicinal compounds introduced at the beginning of Chapter 1. Tamoxifen **3.35**, an anti-oestrogen drug used in the treatment of breast cancer and pheniramine **3.36**, an antihistamine sold under the brand name Avil are two more important dimethylamines which are commercially available (Figure 3.2). The importance of dimethylamines especially in pharmaceuticals is further discussed in Chapter 4.



**Figure 3.2** Examples of dimethylamines in pharmaceuticals.

The success of the ruthenium chemistry described in Section 3.4 and our subsequent interest in the synthesis of dimethylamines by a ruthenium-catalysed synthesis by “borrowing hydrogen” led us to examine the possibility of applying the Ru/dppf catalytic system for this reaction.

#### 3.5.1 Initial Studies

From our previous investigation, we knew that amine acetate can be used in the transformation of a secondary amine to a tertiary amine (Table 3.3). We wished to extend this methodology to dimethylamine as the secondary amine and considering the volatility of dimethylamine (b.p. 7 °C), the use of dimethylamine acetate as the dimethylamine surrogate could potentially lead us to a one-pot synthesis of dimethylamines.

The traditional synthesis of dimethylamines is the *N*-alkylation of dimethylamine already discussed briefly in Chapter 1. Additionally, dimethylamines such as *N,N*-dimethyldodecylamine is an intermediate for cationic surfactants and amphoteric



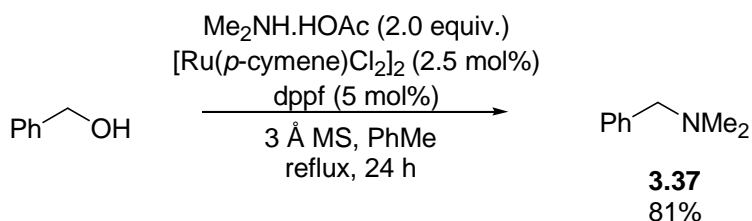
compounds and is produced worldwide by the one-step amination of dodecyl alcohol (ROH) and dimethylamine (HNMe<sub>2</sub>) over Cu/Ni-based solid catalysts (Scheme 3.10).<sup>[19]</sup>



**Scheme 3.10** One-step amination of dodecyl alcohol and HNMe<sub>2</sub> using the Cu/Ni-based solid catalysts.

The main reaction sequence for the RNMe<sub>2</sub> formation consists of three steps: (i) catalytic dehydrogenation of dodecyl alcohol over Cu, (ii) non-catalytic formation of an HNMe<sub>2</sub>-aldehyde adduct and (iii) hydrogenolysis of the adduct to RNMe<sub>2</sub> and water. This conventional Cu/Ni-based solid catalyst requires hydrogen for the amination reaction because it has been considered as a conventional reductive amination of aldehydes, requiring bulk hydrogen. Recently, Cu/Ni-based colloidal have been developed that do not require bulk hydrogen presumably due to the active hydrogen trapped as CuH in dehydrogenation of dodecyl alcohol over reduced copper, was effectively consumed, without the liberation as hydrogen molecules, for the following hydrogenolysis over reduced nickel.<sup>[20]</sup> These methods while efficient, require the use of a continuous supply of dimethylamine gas in a reactor and is therefore not applicable in laboratory synthesis.

Hence, we started our investigations by considering the conversion of benzyl alcohol into *N,N*-dimethylbenzylamine. The dimethylation of benzyl alcohol was carried out with two equivalents of preformed dimethylammonium acetate using 1.25 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (2.5 mol% of Ru) with 2.5 mol% dppe as the diphosphine ligand to give a product **3.37** in 81% isolated yield (Scheme 3.11).



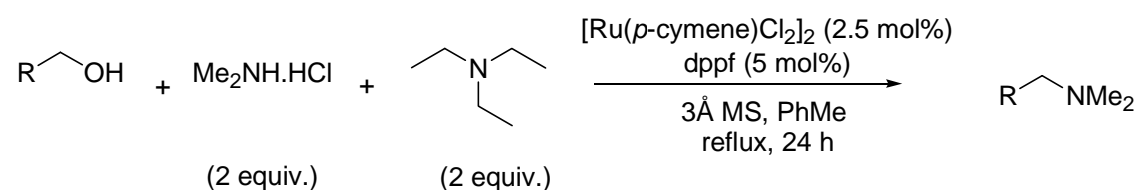
**Scheme 3.11** Dimethylation of benzyl alcohol by “borrowing hydrogen”.

Although this methodology is a viable way to synthesise dimethylamines, we wished to find other dimethylamine surrogates for the reaction as we have found that preforming the dimethylamine acetate is tedious as it is a hygroscopic compound. Next, we set out

several investigations on other dimethylamine surrogates or dimethylamine sources for the reaction.

Firstly, the commercially available dimethylamine hydrochloride was considered in the reaction. We proposed that the use of an equal equivalent of organic base such as triethylamine would be necessary to generate dimethylamine in the reaction. Hence, three reactions were carried out with three alcohols under the “borrowing hydrogen” conditions using triethylamine as the base (Table 3.8).

**Table 3.8** Dimethylation of primary alcohols with dimethylamine acetate by “borrowing hydrogen”.



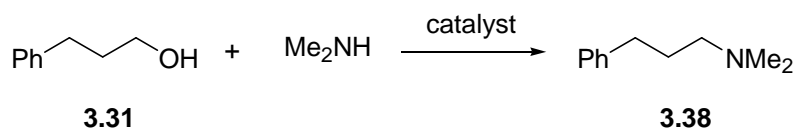
Entry	R	Conversion <sup>[a]</sup> (%)
1	Ph	Side product
2	PhCH <sub>2</sub>	45 <sup>[b]</sup>
3	PhCH <sub>2</sub> CH <sub>2</sub>	100

[a] Reactions carried out on 1 mmol in toluene (1 mL), alcohol:Me<sub>2</sub>NH<sub>2</sub>Cl:Et<sub>3</sub>N (1:2:2), 3 Å MS, 110 °C, 24 h. Conversions are determined by <sup>1</sup>H NMR analysis.

[b] Isolated yield after acid-base extraction.

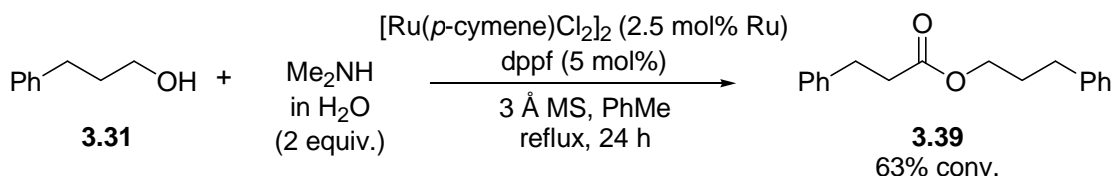
When benzyl alcohol was used in the reaction, the reaction did not go cleanly due to the formation of side products and hence the conversion could not be obtained (Table 3.8, entry 1). Similarly for phenethyl alcohol, the <sup>1</sup>H NMR spectrum of crude material was difficult to interpret and hence an acid-base extraction was carried out to give a modest yield of 45% of clean product (Table 3.8, entry 2). We were pleased to find that when 3-phenylpropanol was used as the alcohol substrate, the reaction went to completion as seen from the <sup>1</sup>H NMR spectrum of crude material (Table 3.8, entry 3). We carried on our investigation on other dimethylamine sources as these results indicated that it is mostly suitable for aliphatic alcohols (Table 3.8, entry 3) and not applicable to benzylic alcohols (Table 3.8, entry 1). Since 3-phenylpropyl alcohol **3.31** gave a full conversion into product (Table 3.8, entry 3), we carried on our investigation by choosing the

reaction of 3-phenylpropyl alcohol **3.31** with dimethylamine to give tertiary amine as a model reaction (Scheme 3.12).



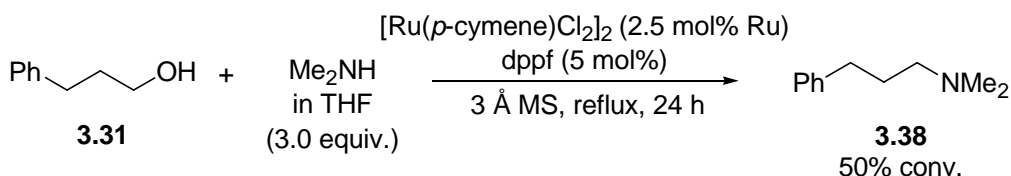
**Scheme 3.12** Dimethylation of 3-phenylpropyl alcohol **3.31**.

Our next approach is the use of commercially available dimethylamine solution (40 wt. % in H<sub>2</sub>O) as the dimethylamine source in the amination of 3-phenylpropyl alcohol **3.31** under the “borrowing hydrogen” conditions (Scheme 3.13). Unfortunately, only ester **3.39** was formed preferentially at 63% conversion as seen from the <sup>1</sup>H NMR spectrum (Scheme 3.12) instead of the desired amine product. We reasoned that the catalyst is deactivated by the presence of water in the reaction.



**Scheme 3.13** Dimethylation of 3-phenylpropyl alcohol using Me<sub>2</sub>NH solution (40 wt. % in H<sub>2</sub>O) by “borrowing hydrogen”.

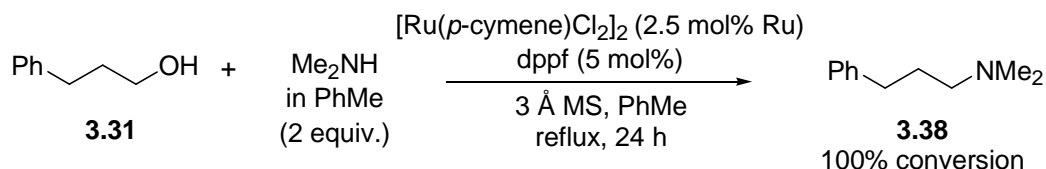
Also commercially available is dimethylamine solution in THF (2.0 M) and a similar reaction was also carried out in the presence of a slight excess of the amount of dimethylamine in the reaction at reflux temperature of THF (Scheme 3.14). We were pleased to find the amine product was formed at a moderate conversion of 50% and only recovered starting alcohol and this is possibly due to the low temperature setting of 75 °C for THF compared to a normal reflux setting of toluene at 110 °C.



**Scheme 3.14** Dimethylation of 3-phenylpropyl alcohol using Me<sub>2</sub>NH solution (2.0 M in THF) by “borrowing hydrogen”.

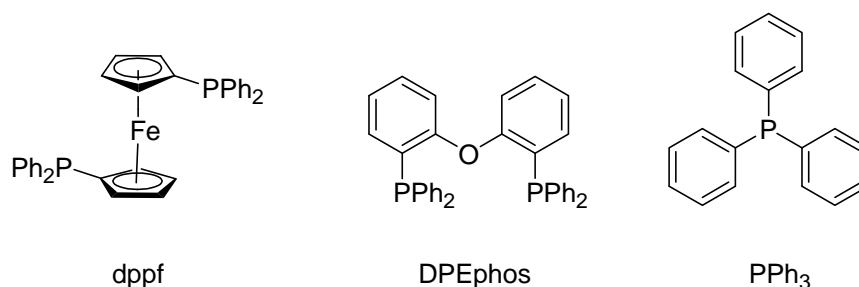
Another interesting approach is to extract dimethylamine into toluene since the “borrowing hydrogen” methodology is carried out in toluene. One way is extracting a dimethylamine solution (40 wt. % solution in H<sub>2</sub>O) with toluene as the extracting solvent. We were pleased to find that after two extractions, 0.56 mmol Me<sub>2</sub>NH/1 mL

toluene mixture was easily obtained. The exact concentration of dimethylamine was then established by comparison of the methyl signals by  $^1\text{H}$  NMR spectroscopy. The dimethylamine toluene solution was then subjected to the “borrowing hydrogen” conditions using 3-phenylpropyl alcohol **3.31** and it underwent clean conversion into the desired product (Scheme 3.15).

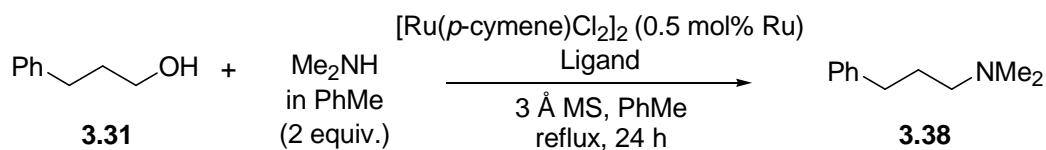


**Scheme 3.15** Dimethylation of 3-phenylpropyl alcohol **3.31** using  $\text{Me}_2\text{NH}$  in toluene by “borrowing hydrogen”.

From all the results obtained so far, the dimethylation of primary alcohols is possible by the “borrowing hydrogen” methodology. Among the dimethylamine sources described, the extraction of dimethylamine into toluene is the most feasible. Hence, an investigation was set out to explore its activity with different ligands at a low catalyst loading of 1 mol% of Ru (Table 3.9) in order to see any variation in the reaction. Three ligands were chosen for this set of screening, namely dppe, DPEphos and  $\text{PPh}_3$  (Figure 3.3). We know that dppe is the diphosphine ligand effective in ruthenium-catalysed *N*-alkylation of both primary and secondary amines and Xantphos gave some product as shown in our earlier screening experiments (Table 2.3, Chapter 2). DPEphos was chosen instead since it is a variant of the Xantphos ligand but is more flexible and  $\text{PPh}_3$  is used because it is a classic example of a monophosphine ligand used in transfer hydrogenation reactions.



**Figure 3.3** Phosphine ligands used in our final ligand screening.

**Table 3.9** Screening of ligand loading for the dimethylamination of 3-phenylpropyl alcohol **3.31**.

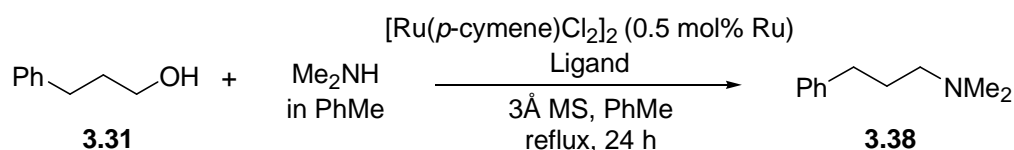
Entry	Ligand	Conversion by <sup>1</sup> H NMR (%)
1	-	22
2	dppf 0.5 mol%	38
3	dppf 1 mol%	40
4	dppf 2 mol%	100
5	DPEphos 0.5 mol%	37
6	DPEphos 1 mol%	50
7	DPEphos 2 mol%	100
8	PPh <sub>3</sub> 0.5 mol%	No Reaction
9	PPh <sub>3</sub> 1 mol%	45
10	PPh <sub>3</sub> 2 mol%	49

[a] Reactions carried out on 1 mmol in toluene (0.5 mL), alcohol:Me<sub>2</sub>NH<sub>2</sub> (1:1), 3 Å MS, 110 °C, 24 h. Conversions are determined by <sup>1</sup>H NMR analysis.

Without the use of ligand, the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> catalyst gave a small amount of product (Table 3.9, entry 1). The results show that all three ligands are effective for the dimethylamination of 3-phenylpropyl alcohol by “borrowing hydrogen” at a catalyst loading of only 0.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>. PPh<sub>3</sub> gave product at only a moderate conversion even at 2 mol% of ligand was used in the reaction (Table 3.9, entry 9). The reactivity of dppf and DPEphos are quite similar to each other as shown by the similar conversions obtained at different ligand loadings (Table 3.9, entries 1-6). Additionally, the use of two equivalents of ligand in the reaction led to clean conversion into the product for both dppf and DPEphos (Table 3.9, entries 3 and 6). Given that DPEphos is considerably cheaper than dppf,<sup>[21]</sup> we chose to run our subsequent reactions with DPEphos. Additionally, the catalytic combination of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and DPEphos has not been used in the amination of alcohols before.

Having established that an excess of ligand improved the reaction to an extent (Table 3.9, entries 7 and 10) it was of interest to know whether the amount of ligand could be reduced without loss of performance. Hence, an investigation into using a slight excess of DPEphos as well as whether the use of molecular sieves is necessary in the reaction were carried out (Table 3.10).

**Table 3.10** Variation of ligand loading and use of 3 Å molecular sieves in the dimethylation of 3-phenylpropyl alcohol **3.31**.<sup>[a]</sup>



Entry	Ligand	3 Å MS	Conversion by <sup>1</sup> H NMR (%)
1	DPEphos 1.2 mol%	Yes	100
2	DPEphos 2 mol%	Yes	100
3	DPEphos 1.2 mol%	No	100
4	DPEphos 2 mol%	No	100

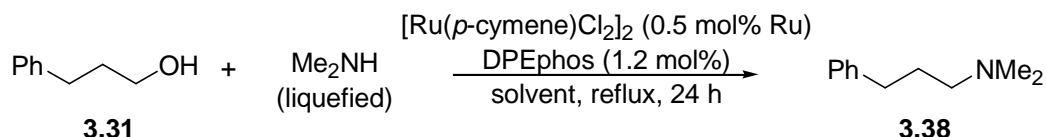
[a] Reactions carried out on 1 mmol in toluene (0.5 mL), alcohol:Me<sub>2</sub>NH<sub>2</sub> (1:1), 3 Å MS, 110 °C, 24 h. Conversions are determined by <sup>1</sup>H NMR analysis.

From these screening conditions, it can be deduced that 1.2 mol% DPEphos is the best ligand loading and the addition of molecular sieves had no obvious beneficial effect on these reactions and was omitted in future experiments (Table 3.10, entry 4). Hence, the highest yield obtained for the dimethylation of 3-phenylpropyl alcohol is 0.5 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  and 1.2 mol% of DPEphos under the “borrowing hydrogen” conditions.

Although it was convenient to prepare the dimethylamine in toluene solution by extraction methods, it was proposed that since dimethylamine gas has a boiling point of 7 °C, theoretically, liquefying the gas using an acetone/dry ice mixture, followed by the addition of toluene into the tube should lead us to the preparation of a dimethylamine in toluene mixture and could therefore be used in the dimethylation by “borrowing hydrogen”.

The first investigation carried out was the use of liquefied dimethylamine gas in the dimethylation reaction of 3-phenylpropyl alcohol **3.31** in the presence of various solvents (Table 3.11).

**Table 3.11** Dimethylation reaction of 3-phenylpropyl alcohol **3.31** in the presence of various solvents.



Entry	Solvent <sup>[a]</sup>	Conversion by <sup>1</sup> H NMR (%) <sup>[b]</sup>
1	Neat	92
2	Toluene [4.0 mL]	No Reaction
3	Toluene (2 mol% DPEphos) [1.5 mL]	23
4	Hexane [2.0 mL]	No Reaction
5	Amyl alcohol [2.0 mL]	No Reaction
6	DMF [5.0 mL]	No Reaction
7	DMSO [4.0 mL]	No Reaction
8	DCE [1.5 mL]	No Reaction, side products seen
9	1,4-Dioxane [1.5 mL]	No Reaction
10	THF [1.5 mL]	41
11	Heptyl cyanide [1.5 mL]	No Reaction
12	Diisopropyl ether [2.0 mL]	No Reaction
13	Acetonitrile [2.0 mL]	No Reaction

[a] The values in parentheses are the total amount of solvent and liquefied Me<sub>2</sub>NH used in mL.

[b] Reactions carried out on 0.06 mmol of alcohol, 110 °C, 24 h. Conversions are determined by <sup>1</sup>H NMR analysis.

We originally planned to use a cold syringe to inject 0.05 mL of liquefied dimethylamine (1.5 equiv. to alcohol) into individual tubes respectively but it proved to be a difficult procedure since it vapourised upon exposure to room temperature. Finally, it was added directly from the dimethylamine gas cylinder and liquefied straight

to each tube respectively. It was difficult to control the amount of liquefied dimethylamine added and hence the total amount of solvent and liquefied dimethylamine used for reaction tubes is different (shown in parentheses). Disappointingly, most of the reactions gave negative results. However, the reaction can be performed without any need of solvent (Table 3.11, entry 1). Toluene and THF are the only two solvents that gave reasonable conversions (Table 3.11, entries 3 and 10).

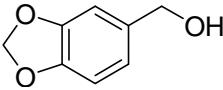
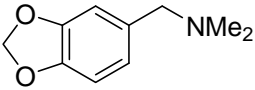
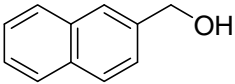
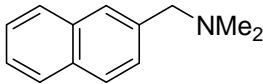
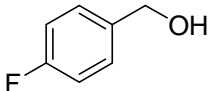
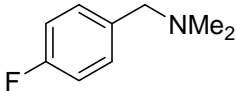
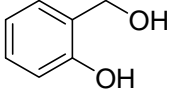
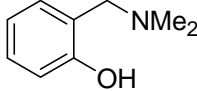
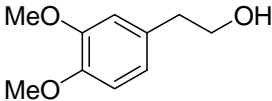
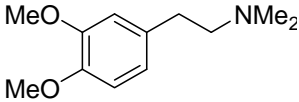
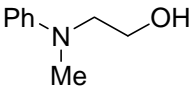
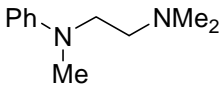
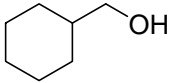
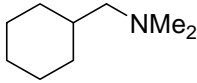
Our next strategy is to prepare a Me<sub>2</sub>NH/toluene mixture using the liquefied dimethylamine gas. For example, to obtain approximately 1.39 M of dimethylamine in toluene, dimethylamine (1.64 mL) was liquefied at -78 °C and toluene (20 mL) was injected into it and the exact concentration of dimethylamine was then established by comparison of the methyl signals by <sup>1</sup>H NMR spectroscopy. The concentration of Me<sub>2</sub>NH/toluene mixture is typically 1-1.5 mmol per mL and this preparation has been used in future experiments.

### 3.5.2 Ruthenium-Catalysed Synthesis of *N,N*-Dimethylamines from Alcohols by Borrowing Hydrogen

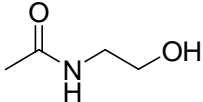
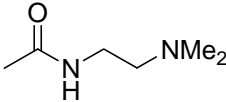
Using the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>/DPEphos combination, we then investigated the scope of the reaction using other alcohols which were converted into the corresponding dimethylamino compounds (Table 3.12). For simple substrates, the catalyst loading could be as low as 0.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (*i.e.* 1 mol% in Ru).



**Table 3.12** Dimethylamination reaction of different primary alcohols.

$\text{R-CH}_2\text{OH} + \text{Me}_2\text{NH} \xrightarrow[\text{PhMe, reflux, 24 h}]{\begin{matrix} [\text{Ru}(p\text{-cymene})\text{Cl}_2]_2 \\ \text{DPEphos} \end{matrix}} \text{R-CH}_2\text{NMe}_2$				
Entry	Starting Alcohol	Amine Product	Catalyst (mol%) <sup>[a]</sup>	Yield (%) <sup>[b]</sup>
1	Ph-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH <b>3.31</b>	Ph-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub> <b>3.38</b>	0.5	83 (100)
2	 <b>3.26</b>	 <b>3.40</b>	0.5	85 (96)
3	 <b>2.43</b>	 <b>3.41</b>	0.5	97 (100)
4	 <b>3.42</b>	 <b>3.43</b>	0.5	60 (100)
5	 <b>3.44</b>	 <b>3.45</b>	0.5	88 (100)
6	 <b>2.45</b>	 <b>3.46</b>	0.5	87 (100)
7	 <b>3.47</b>	 <b>3.48</b>	1.25	75 (88)
8	 <b>3.29</b>	 <b>3.49</b>	1.25	77 (100)

**Table 3.12** (*continued*)

Entry	Starting Alcohol	Amine Product	Catalyst (mol%) <sup>[a]</sup>	Yield (%) <sup>[b]</sup>
9	C <sub>8</sub> H <sub>17</sub> OH	C <sub>8</sub> H <sub>17</sub> NMe <sub>2</sub>	1.25	76 (100)
	<b>3.50</b>	<b>3.51</b>		
10	Ph-O-CH <sub>2</sub> -CH <sub>2</sub> -OH	Ph-O-CH <sub>2</sub> -CH <sub>2</sub> -NMe <sub>2</sub>	2.5	77 (96)
	<b>3.52</b>	<b>3.53</b>		
11			2.5	72 (100)
	<b>3.54</b>	<b>3.55</b>		

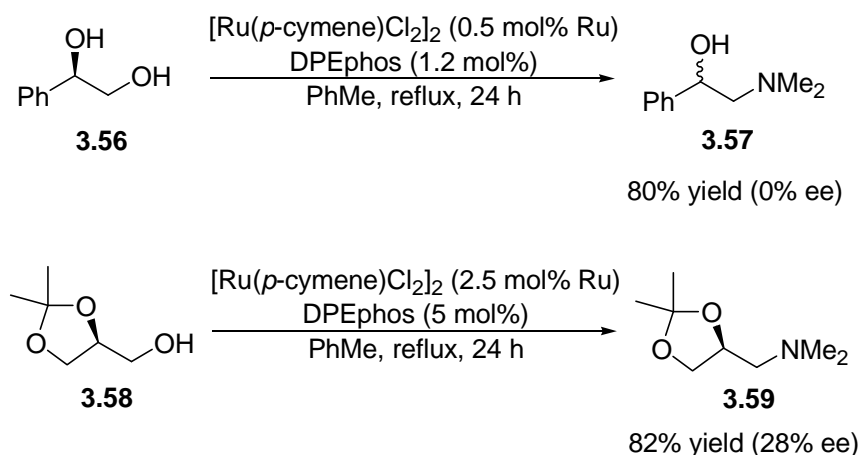
[a] 0.5 mol% of the dimer is equivalent to 1 mol% Ru. DPEphos was added (1.2 mol% for entries 1-6, 2.5 mol% for entries 7-9, 5 mol% for entries 10, 11).

[b] Isolated yields after column chromatography. The values in parentheses indicate conversions determined by analysis of the <sup>1</sup>H NMR spectrum.

We were pleased to find that most alcohols were converted cleanly into the corresponding *N,N*-dimethylamines. Benzylic alcohols (Table 3.12, entries 2-5) readily underwent this transformation, even for the ortho-substituted phenol (Table 3.12, entry 5). We had some concerns that the position of the heteroatom in entries 7 and 10 could lead to problems because the presumed intermediate aldehyde is relatively unstable and therefore harder to form in the initial oxidation step. However, these reactions were achieved successfully. Simple aliphatic substrates were also converted into product (Table 3.12, entries 8 and 9). In a few cases (Table 3.12, entries 4, 8, 9) the isolated yield was lower than might have been expected from the purity of the crude material judged by the <sup>1</sup>H NMR spectrum, and the relative volatility of these products may have contributed to losses during removal of solvents.

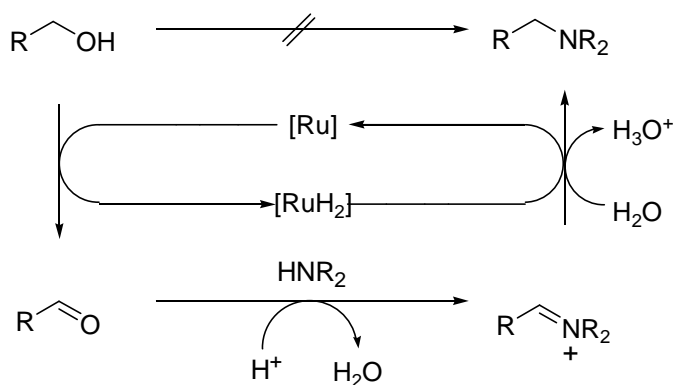
The use of enantiomerically pure compounds **3.56** and **3.58** was also examined for their ability to undergo transformation into the corresponding dimethylamino compounds (Scheme 3.16). Diol **3.56** is an interesting substrate since although secondary alcohols are thermodynamically more readily oxidised, the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> /DPEphos combination requires more forcing conditions for the amination of secondary alcohols.<sup>[22]</sup> Only amination of the primary alcohol is observed to give amino alcohol **3.57**, although the fact that racemic product is formed could suggest that the secondary alcohol undergoes reversible oxidation to the ketone<sup>[23]</sup> or *via* enolization of the

intermediate aldehyde. In the case of substrate **3.58**, the majority of the stereochemical purity is lost during the amination reaction, presumably *via* racemisation of the intermediate aldehyde or iminium species.<sup>[24]</sup>



**Scheme 3.16** Dimethylamination of enantiomerically pure substrates by “borrowing hydrogen”.

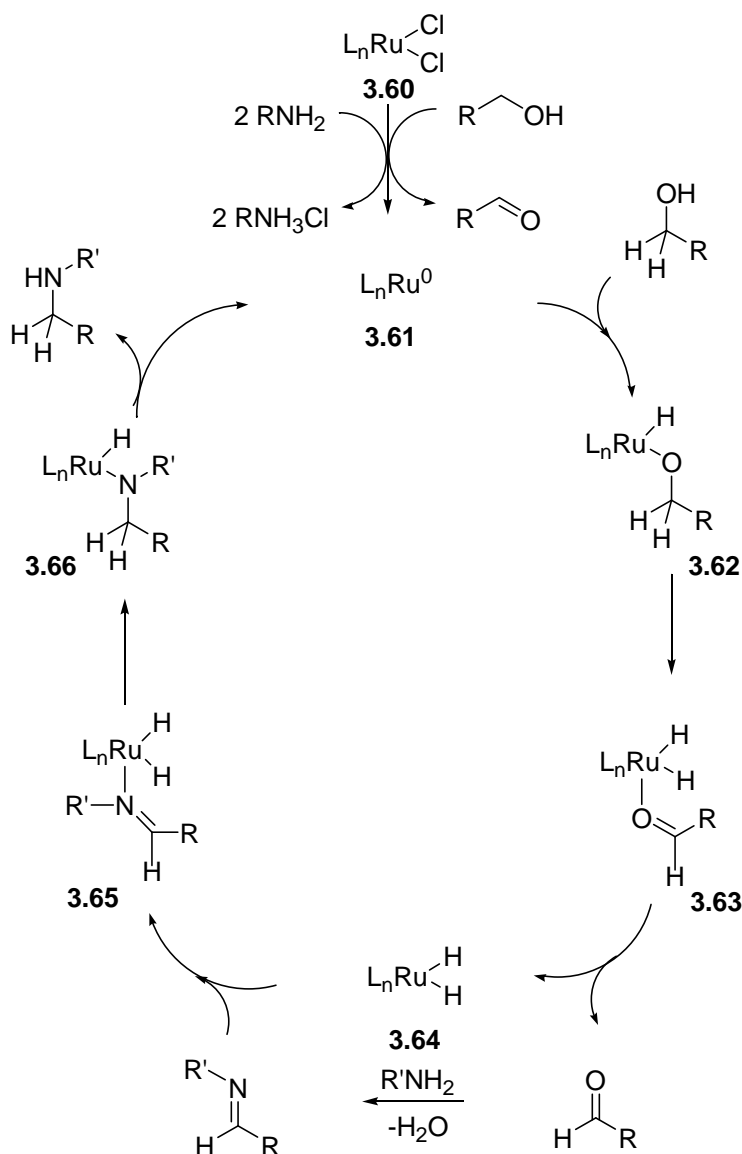
The “borrowing hydrogen” strategy in the formation of tertiary amines is shown in Scheme 3.17. The removal of hydrogen from the alcohol temporarily gives an aldehyde, which in turn reacts with the amine to give an intermediate iminium species, which is converted into the tertiary amine by the return of the hydrogen. It is also possible that the enamine could also be involved as an intermediate in the reaction but not in cases when R is aryl.



**Scheme 3.17** Tertiary amine formation by “borrowing hydrogen”.

A plausible mechanism for the alkylation of an amine by alcohol on the whole using the  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ /diphosphine combination is depicted in Scheme 3.18. Complexation of a diphosphine with the ruthenium would lead to the formation of the cationic 18 electron complex  $[\text{Ru}(\text{P-P})(p\text{-cymene})\text{Cl}]\text{Cl}^{[25]}$  which needs to create a free co-ordination site to become catalytically active. The Williams group<sup>[26]</sup> has previously

shown that the reaction of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  with BINAP and the diamine DPEN leads to the formation of the Noyori complex  $[\text{Ru}(\text{BINAP})(\text{DPEN})\text{Cl}_2]^{[27]}$  and it is believed that the *p*-cymene is dissociated in the active complex. *p*-Cymene is also sometimes observed in the crude  $^1\text{H}$  NMR spectra at the end of *N*-alkylation reactions. Hence, we proposed that the complex **3.60** is generated where  $\text{L}_n$  represents the bidentate phosphine and probably amine ligands. Activation of complex **3.60** can be considered to give a ruthenium(0) complex **3.61** *via* exchange of a chloride with alkoxide, and loss of HCl.  $\beta$ -Hydride transfer from the alkoxy complex to give  $\text{L}_n\text{RuHCl}(\text{O}=\text{CHR})$  then leads to complex **3.61** by loss of the aldehyde and HCl. Oxidative addition of the alcohol provides the alkoxy hydride complex **3.62**, which subsequently undergo  $\beta$ -hydride transfer to form the aldehyde complex **3.63**. The imine complex **3.65** is formed by dissociation of the aldehyde, imine formation and re-complexation, presumably by the dihydride complex **3.64**.  $\beta$ -Hydride transfer to give the amido complex **3.66** and reductive elimination affords the amine product and regenerates the ruthenium(0) complex **3.61**. When the reaction involves the *N*-alkylation of a secondary amine, the intermediate iminium species would not be able to bind through the nitrogen, and the reaction could proceed either *via* an  $\eta^2$  iminium complex, or *via* the enamine.



**Scheme 3.18** Mechanistic proposal for the *N*-alkylation of alcohols with amines.

### 3.6 Chapter Summary

The attempted synthesis of primary amines by “borrowing hydrogen” strategy was not successful. It was found that the  $[Ru(p\text{-cymene})Cl_2]_2/dppf$  combination is highly efficient for the *N*-alkylation of secondary amines with primary alcohols by “borrowing hydrogen”. This methodology has been applied to the one pot synthesis of Piribedil (*vide infra*, Chapter 4) and other piperazine and morpholine-containing products. The results of this study have been published.<sup>[28]</sup> The “borrowing hydrogen” strategy has also been applied to the synthesis of a range of dimethylamines whereby in the case of simple substrates, the catalyst loading could be as low as 0.5 mol%  $[Ru(p\text{-cymene})Cl_2]_2$  (*i.e.* 1 mol% in Ru). An application of this methodology is discussed in the following chapter whereby some antihistamine agents were synthesised successfully (*vide infra*,

Chapter 4). The mechanism for the *N*-alkylation of alcohols with amines is also proposed.

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# Chapter 4

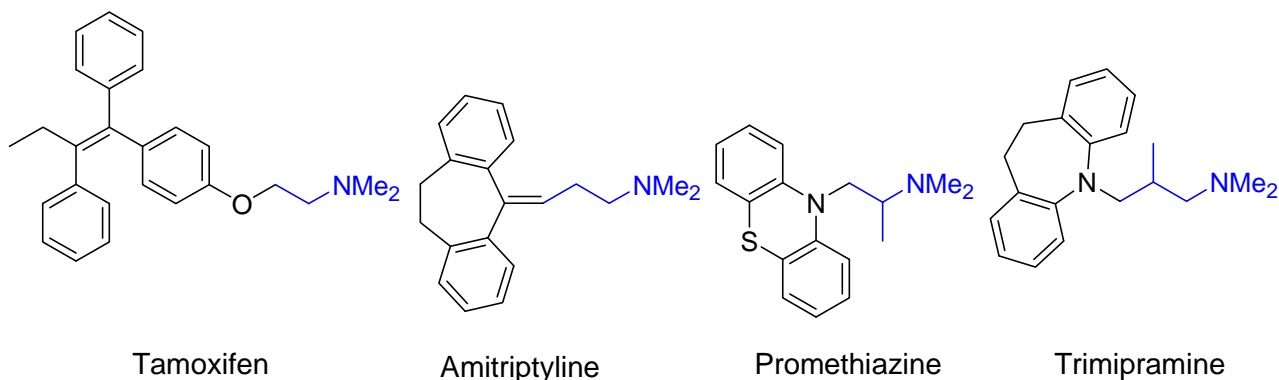
## 4. Application

Amines have found many applications in the areas of agrochemicals, dyestuffs, pharmaceuticals, surfactants, plastics, chemical auxiliaries (*e.g.* for rubber, textiles and paper manufacture), anti-corrosion agents and as process chemicals.<sup>[1]</sup>

### 4.1 Introduction

The preparation of amines is an important synthetic method and catalytic approaches using alcohols as starting materials would have significant potential benefits for industrial scale reactions.<sup>[2]</sup> Pharmaceutical drug companies in particular, have considerable interest in developing efficient protocols that are green, atom-efficient and avoid multi-step procedures and the use of genotoxic substrates.

The majority of pharmaceuticals contain an acyclic pendant side chain, often containing a terminal amine or a carboxylic acid group, attached to a cyclic or heterocyclic group.<sup>[1]</sup> Examples of the side chains found in some pharmaceuticals are shown in Figure 4.1.



**Figure 4.1** Side chains (in blue) found in some pharmaceuticals.

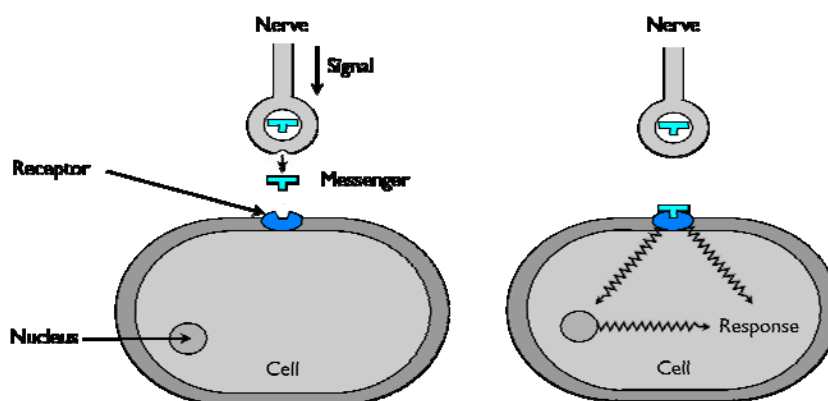
The above pharmaceuticals have a common pharmacophore, the *N,N*-dimethylamino group. It is found as a side chain in 24 marketed drugs covering most therapeutic applications.<sup>[3]</sup> Some important applications include use in antibiotics, antihelminthics, CNS drugs, anti-fungals and in neoplastic chemotherapy. Some of the advantages of this group and other amine-based side chains are: they are relatively easy to attach to the substrate compound with a readily available precursor, they are stable under



physiological conditions and they are resistant to self-alkylation and metabolism. The presence of an amine side chain provides two functions in medicine: to assist the pharmaceutical to be transported to the target site in the body and then to lock onto the desired receptor.<sup>[1]</sup>

## 4.2 The Role of the Receptor

Drugs that interact with receptors are very important in medicine since they provide treatment for ailments such as pain, depression, Parkinson's disease, heart failure, asthma and many others.<sup>[4]</sup> The brain and spinal column (the central nervous system) are responsible for control and communication within a body. Messages are received and sent *via* a network of nerves. However, nerves do not connect directly to their target cells but release a chemical messenger from the nerve cell called a neurotransmitter (Figure 4.2).



**Figure 4.2** Neurotransmitter action, adapted from ref. 4.

Once released, the neurotransmitter diffuses across the gap to the target cell where it binds and interacts with a specific protein (receptor) implanted in the cell membrane. This process of binding leads to either a flow of ions across the cell membrane or in switching on (or off) of enzymes within the target cell. Hence, the communication system depends essentially on a chemical messenger. As a chemical process is involved, other chemicals (drugs) should be able to interfere or interact with the process.<sup>[4]</sup>

Communication is essential for the normal working of a human body and failure in communication could lead to chronic conditions such as depression, heart problems, schizophrenia, muscle fatigue, and many others. In such cases, the problem could arise

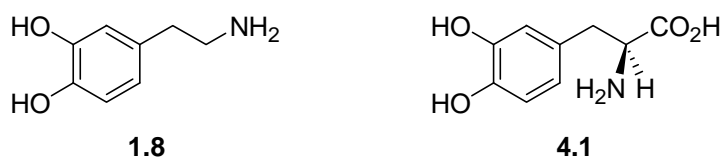
from having too many messengers released at a time and the target cell could (metaphorically) start to overheat. On the other hand, if too few messengers were sent out, the cell could become slow-moving. In either situation, drugs can play a role by acting as replacement messengers also known as **agonists**; or by blocking the receptors for the natural messengers known as **antagonists**.<sup>[4]</sup>

### 4.3 Agonists

An agonist is a substance that interacts with the receptor, and elicits an observable biological response.<sup>[5]</sup> It may be a neurotransmitter or hormone that occurs naturally within the body, or it can be an exogenous substance such as a synthetic drug. Agonists generally have a structure similar to the natural ligand for the receptor. There are also partial agonists that act on the same receptor as other agonists in a group of ligands or drugs,<sup>[5]</sup> however, they only induce a weaker effect than a full agonist.<sup>[4]</sup>

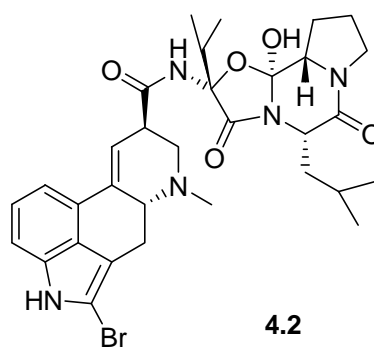
Dopamine **1.8**, a phenylethylamine, was first discovered by Arvid Carlsson and Nils-Åke Hillarp at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden in 1952 (Figure 4.3). The significance of this compound has advanced from an intermediate in noradrenaline synthesis, in 1957, to its position as a major neurotransmitter in the brain at present.<sup>[6]</sup> In the brain, dopamine activates five types of dopamine receptors i.e. D1, D2, D3, D4 and D5, and their variants.

Dopamine deficiency leads to Parkinson's disease which is the second most common neurodegenerative disease and in the United States alone, more than 500,000 people are affected.<sup>[7]</sup> It is characterised by chronic, progressive motor dysfunction resulting in severe tremors, difficulty in initiating movement, rigidity, speech and swallowing difficulties.<sup>5</sup> This is an incurable and slow progressing disease leading to invalidism. Logically, dopamine replacement therapy would be presumed to be the treatment for Parkinson's disease. However, dopamine **1.8** cannot cross the blood-brain barrier since it is too polar. Dopa-responsive dystonia, L(-)-Dopa (levodopa **4.1**), the precursor of dopamine, is even more polar but it is also an amino acid. Therefore, it is recognised by the carrier proteins for amino acids which carry it across the cell membrane.<sup>[4]</sup>



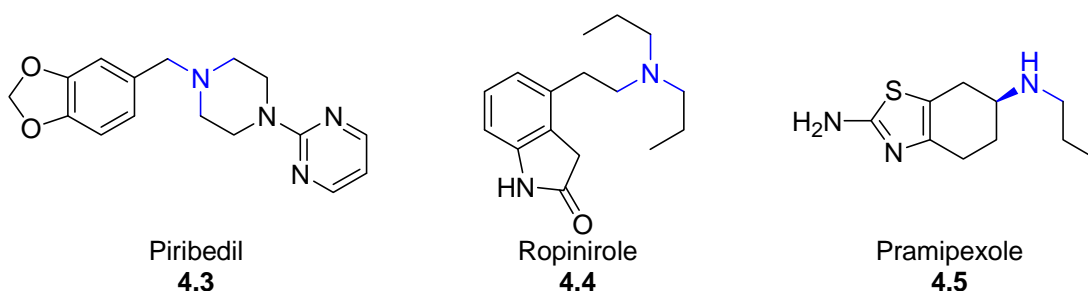
**Figure 4.3** *Dopamine and Levodopa.*

Although levodopa therapy improves motor symptoms of patients with Parkinson's disease, the occurrence of motor fluctuations and dyskinesias creates a major therapeutic challenge.<sup>[8]</sup> Dopamine agonists were initially thought to be effective only as an additional therapy to levodopa, until recently they were accepted as primary treatment in early Parkinson's disease with a decrease in the occurrence of dyskinesia.<sup>[9]</sup>



**Figure 4.4** *Structure of Bromocriptine.*

Bromocriptine **4.2** was the first oral ergot (fungus origin) compound approved as a dopamine agonist and other ergot and non-ergot-derived dopamine agonists have been subsequently developed and used (Figure 4.4). Several examples of non-ergot alkaloid dopamine agonists (**4.3**, **4.4**, **4.5**) used in the treatment of Parkinson's disease are shown in Figure 4.5.

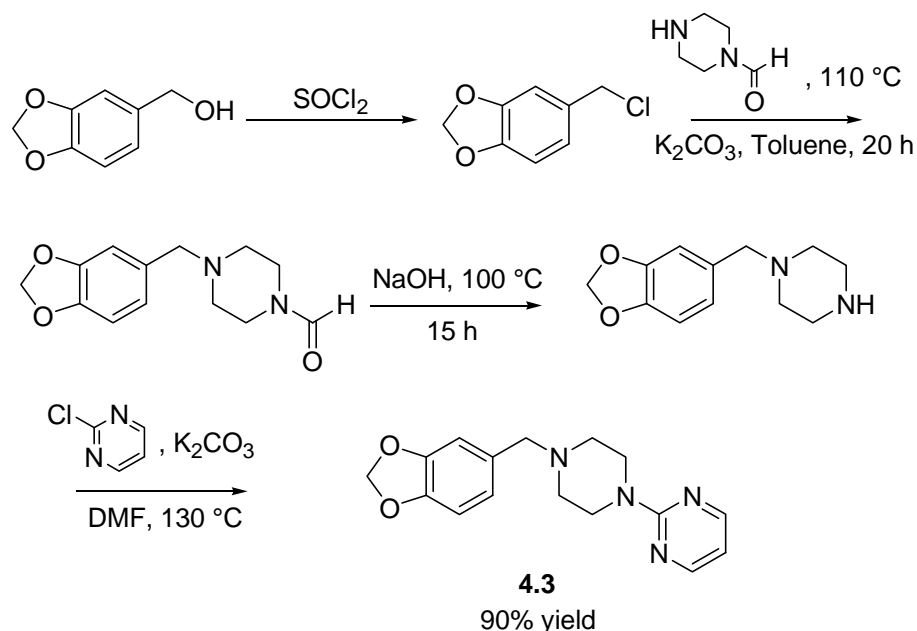


**Figure 4.5** *Structures of non-ergot alkaloid dopamine agonists used in the treatment of Parkinson's disease (Piribedil, Ropinirole, Pramipexole).*

### 4.3.1 Synthesis of Piribedil

Piribedil {2-[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]pyrimidine, Trivastal®} **4.3** is a centrally acting dopamine agonist that stimulates post-synaptic dopamine D2 and D3 receptors.<sup>[10]</sup> Piribedil **4.3** has been shown to improve parkinsonism induced by the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in marmoset monkeys. Rondot and Ziegler reported that in clinical trials, Piribedil **4.3** alleviated the cardinal features of Parkinson's disease when used as monotherapy in *de novo* Caucasian patients.<sup>[11]</sup> Also, in non-fluctuating Parkinson's disease patients insufficiently controlled by levodopa, add-on Piribedil therapy was shown to significantly improve motor symptoms compared to placebo.<sup>[12]</sup> Currently, Piribedil **4.3** is marketed in Asia and Europe.<sup>[13]</sup>

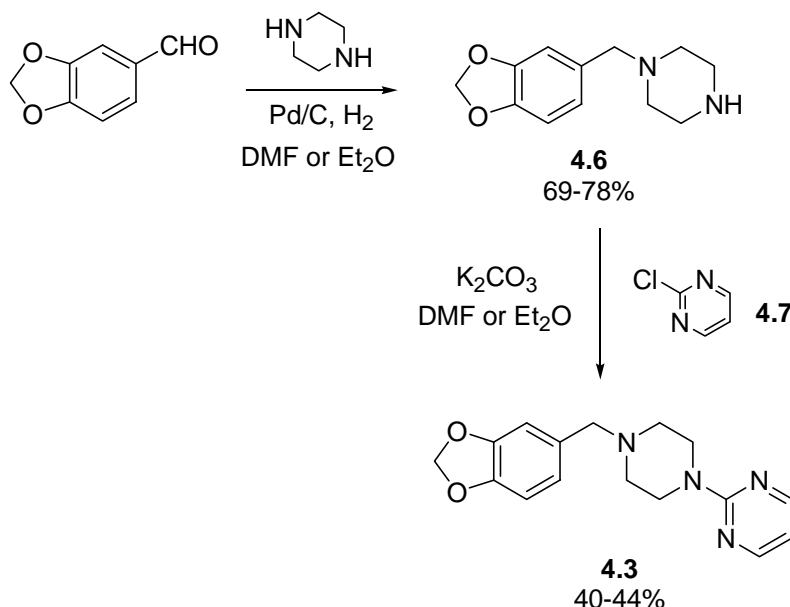
There are many different syntheses of Piribedil **4.3** described in the literature. One of the earliest examples is shown in Scheme 5.1. In this synthesis, 2-chloropyrimidine and 1-piperonylpiperazine are condensed in excess of anhydrous K<sub>2</sub>CO<sub>3</sub> (3 equiv.) in DMF at a temperature of 130 °C.<sup>[14]</sup> A yield of 90% was obtained and several methods describing the synthesis of Piribedil **4.3** have since been reported.



**Scheme 4.1** Synthesis of Piribedil by Regnier, G. L. et al.

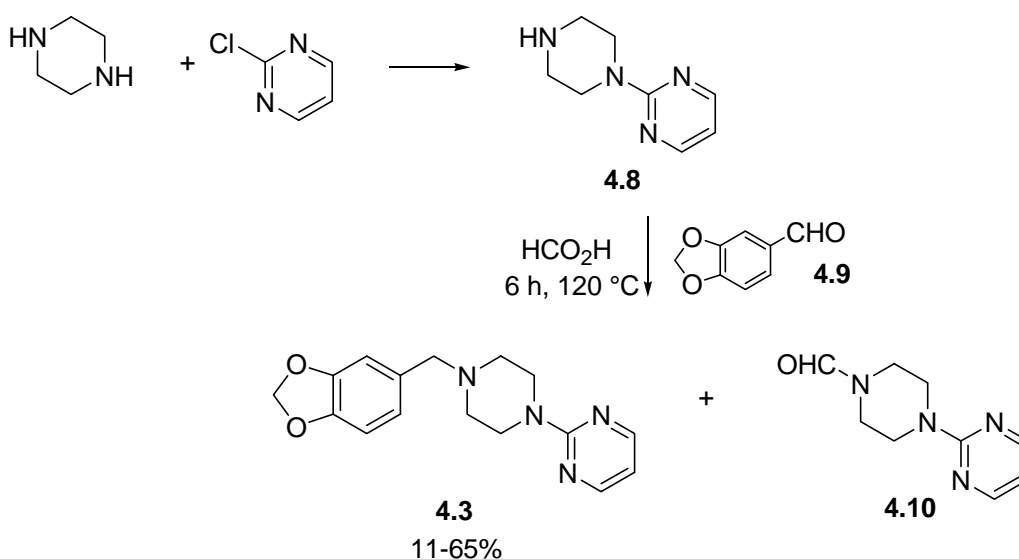
Recently, Yanlong Kang<sup>[15]</sup> from the Beijing Venturepharm Laboratories Limited described a process synthesis of Piribedil **4.3** that utilises a reductive amination reaction in the first step followed by condensation of piperonyl piperazine **4.6** with 2-

chloropyrimidine **4.7** in the presence of excess  $K_2CO_3$  in different solvents (Scheme 4.2). A large-scale synthesis was carried out and Piribedil was obtained in modest yields.



**Scheme 4.2** Synthesis of Piribedil by Yanlong Kang, Beijing Venturepharm Laboratories Limited.

Chilmonczyk *et al.*<sup>[16]</sup> developed a synthesis of Piribedil based on the *Leuckart-Wallach* reaction of 1-(2-pyrimidyl)piperazine **4.8** with piperonal **4.9** in the presence of excess formic acid obtaining yields of 11% to 65% depending on the reaction conditions. In the described synthesis (Scheme 4.3), 1-formyl-4-(2-pyrimidyl)piperazine **4.10** was also obtained as a side product presumably formed from the *N*-formylation of 1-(2-pyrimidyl)piperazine **4.8**. This method is recognised as the simplest method for the preparation of Piribedil to date.<sup>[17]</sup>



**Scheme 4.3** Synthesis of Piribedil by Chilmonczyk *et al.*

In general, conventional syntheses of Piribedil **4.3** involve the use of toxic and corrosive alkylating reagents or carbonyl compounds and the generation of wasteful salts as by-products are undesirable environmentally. Additionally, drastic conditions such as basic conditions are needed for the *N*-alkylation steps to proceed. Recent literature procedures<sup>[15]</sup> use reductive amination methods requiring use of stoichiometric amount of acid or high-pressure equipment and only moderate yields are obtained. Herein, we develop<sup>[18]</sup> an application of the ruthenium-catalysed *N*-alkylation of secondary amines via “borrowing hydrogen” (Chapter 3.4) in the synthesis of Piribedil **4.3**.

### 4.3.2 Ruthenium-Catalysed Synthesis of Piribedil by Borrowing Hydrogen

A careful consideration of the structure of Piribedil **4.3** reveals a tertiary amine functional group. Disconnection of Piribedil **4.3** leads to readily accessible substrates that are piperonyl alcohol **3.26** and 1-(2-pyrimidyl)piperazine **4.8** (Figure 4.6).

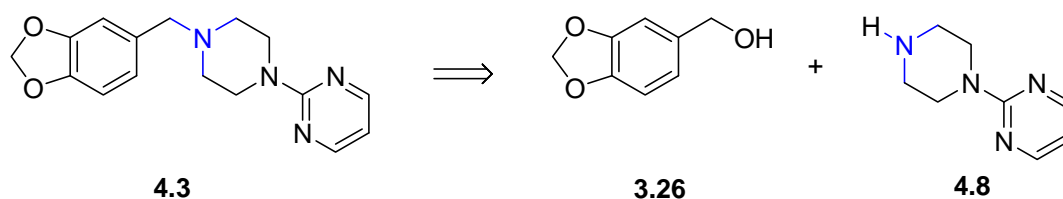
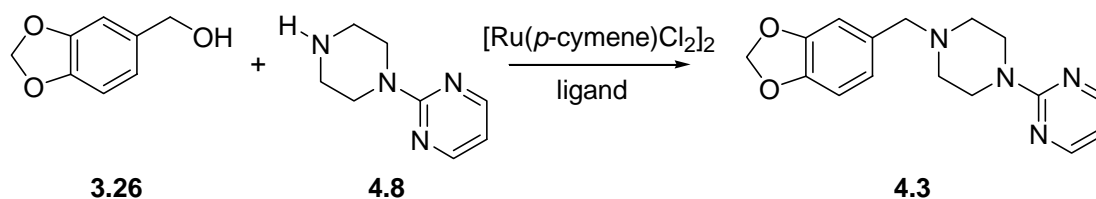


Figure 4.6 Retrosynthesis of Piribedil.

We had previously optimised conditions for the synthesis of tertiary amine employing 1.25 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and 2.5 mol% dppf in refluxing toluene for 24 hours (Chapter 3.4). We applied these optimised conditions to the synthesis of Piribedil **4.3**. A screening of catalyst loading and use of different ligands was also carried out (Table 4.1).

**Table 4.1** Screening of catalyst and ligand for Piribedil synthesis<sup>[a]</sup>

Entry	[Ru] loading	Ligand/loading	Conv. (%) <sup>[b]</sup>	Product	Aldehyde
1	-	Dppf/2.5 mol%	-	-	-
2	-	DPEphos/2.5 mol%	-	-	-
3	2.5 mol%	-	38	38	-
4	2.5 mol%	Dppf/2.5 mol%	100	100	-
5	2.5 mol% <sup>[c]</sup>	Dppf/2.5 mol%	75	69	6
6	1 mol%	Dppf/1 mol%	18	18	-
7	2.5 mol%	DPEphos/2.5 mol%	100	93	7
8	2.5 mol% <sup>[c]</sup>	DPEphos/2.5 mol%	100	93	7
9	1 mol%	DPEphos/1 mol%	91	80	11

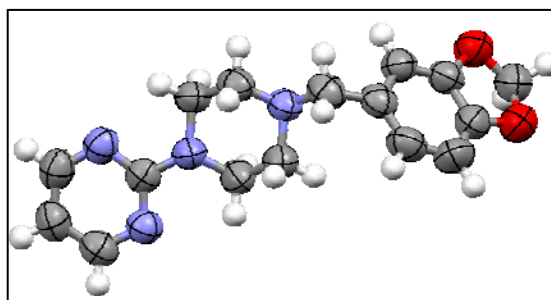
[a] The reactions were carried out in toluene (1.0 mL) at 110 °C for 24 h with piperonyl alcohol (1.0 mmol) and pyridyl piperazine (1.0 mmol).

[b] Conversion determined by analysis of the <sup>1</sup>H NMR spectrum.

[c] Reactions carried out in the presence of 5 mol% of K<sub>2</sub>CO<sub>3</sub> as base.

The ruthenium catalyst is necessary for the reaction to go as shown in entries 1 and 2 (Table 4.1). The  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  catalyst provided some product (Table 4.1, entry 3) but as expected, the catalytic system  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}$  at 2.5 mol% of Ru without base gave the best conversion into Piribedil (Table 4.1, entry 4). A lower catalyst loading of 1 mol% gave a lower conversion into product (Table 4.1, entry 6) and the presence of base led to a lower conversion into product (Table 4.1, entry 5). The  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{DPEphos}$  combination gave a good conversion but had some activity towards the formation of the aldehyde formed from the oxidation of piperonyl alcohol **4.11** (Table 4.1, entries 7-9).

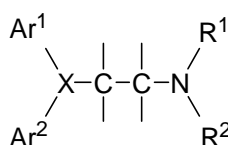
Hence, Piribedil was isolated at a yield of 87% (Table 4.1, entry 4) and the product was easily crystallised from ethanol. Single crystal X-ray diffraction gave the structure illustrated in Figure 5.7 (Crystal data presented in Appendix B).



**Figure 4.7** The crystal structure of Piribedil (from MeOH, m.p. 95-96 °C).

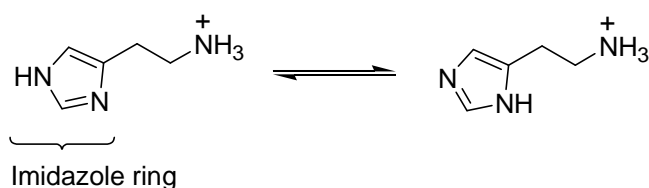
#### 4.4 Antihistamines of H<sub>1</sub> Receptor Antagonists

Many antihistamines have a common pharmacore shown below (Figure 4.8) whereby Ar<sup>1</sup> is aryl, such as phenyl, substituted phenyl, or heteroaryl (2-pyridyl or thienyl) and Ar<sup>2</sup> is aryl or arylmethyl. The two aryl groups can also be connected through a bridge and the CH<sub>2</sub>CH<sub>2</sub>N group can be part of another ring. The tertiary amino groups contain a dimethylamino or pyrrolidino group.<sup>[7]</sup>



**Figure 4.8** Common pharmacore of antihistamines.

These compounds are called antihistamines since they are antagonists of a histamine receptor known as the H<sub>1</sub> histamine receptor. More commonly, the term antihistamine refers only to H<sub>1</sub> antagonists which are also known as H<sub>1</sub> antihistamines. When an allergen is exposed to a sensitised person, an antibody is produced, an antigen-antibody reaction occurs, hence histamine is released.<sup>[7]</sup> Histamine is made up of an imidazole ring which can exist in two tautomeric forms (Figure 4.9). Attached to the imidazole ring is a two-carbon chain with a terminal α-amino group.<sup>[4]</sup>

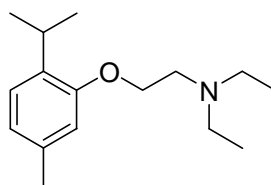


**Figure 4.9** Histamine.



Histamine binding to the  $H_1$  receptor can stimulate the dilatation and increased permeability of small blood vessels. This causes the fluids from the blood to escape into surrounding tissues that are responsible for the itching “runny nose” and watery eyes of a cold or hayfever as the histamine tries to remove the allergen. Antihistamines are generally used to alleviate these symptoms whereby, the tertiary amino groups get protonated and hence, it is thought that the ionic interaction with the receptor is a key binding contributor.<sup>[7]</sup> However, antihistamine cannot displace the histamine if it is already bound.

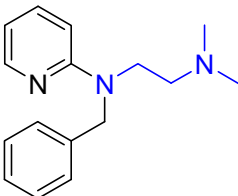
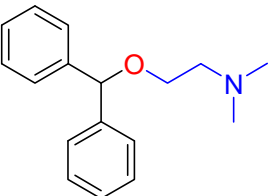
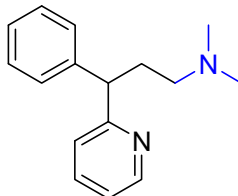
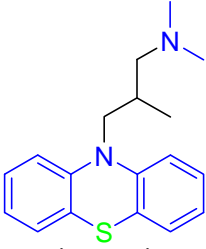
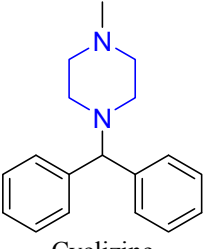
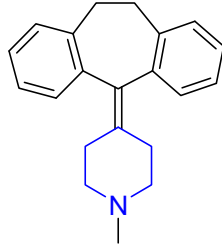
The first compound reported as an antihistamine was the adrenolytic benzodioxan, piperoxan (933F) by Ungar, Parrot and Bovet<sup>[19]</sup> in 1937, which blocked the effect of histamine on the guinea-pig ileum. Subsequently, Bovet & Staub<sup>[20]</sup> (1937) observed that compound F929 **4.11** (2-isopropyl-5-methylphenoxyethyldiethylamine or thymoethyl-diethylamine) protected the guinea pig against histamine in doses high enough to be presumed lethal (Figure 5.10). It was discovered that certain chemicals counteracted the reactions of histamine in guinea pigs. For this research, Swiss-Italian pharmacologist Daniel Bovet was awarded the Nobel Prize for Physiology or Medicine in 1957.<sup>[19]</sup> However, it proved unsuitable for clinical use in humans due to weakness and toxicity, but the pursuit of a histamine-blocking agent suitable for clinical use began.



**4.11**

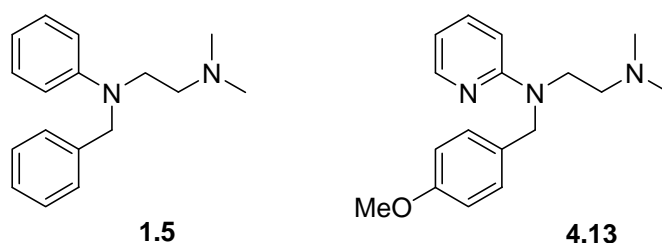
**Figure 4.10** Structure of F929 discovered by Bovet & Staub.

Antihistamine development started from the original compound F929 **4.11**. There are six classes of the antihistamines namely, ethylenediamines, ethanolamines, alkylamines, phenothiazines, piperazines and piperidines (Table 5.2).<sup>[21]</sup>

<p><b>Ethylenediamines</b></p>  <p>Tripeleennamine <b>1.6</b> Others: Mepyramine, Antazoline, Methapyrilene</p>	<p><b>Ethanolamines</b></p>  <p>Diphenhydramine <b>4.12</b> Others: Carbinoxamine, Doxylamine, Clemastine</p>	<p><b>Alkylamines</b></p>  <p>Pheniramine Others: Brompheniramine, Tripolidine, Pyrrobutamin</p>
<p><b>Phenothiazines</b></p>  <p>Trimeprazine Others: Promethazine, Methdilazine</p>	<p><b>Piperazines</b></p>  <p>Cyclizine Others: Chlorcyclizine, Thiethylperazine, Buclizine</p>	<p><b>Piperidines</b></p>  <p>Cyproheptadine Others: Azatadine</p>

**Table 4.2** *Classes of Antihistamines.*

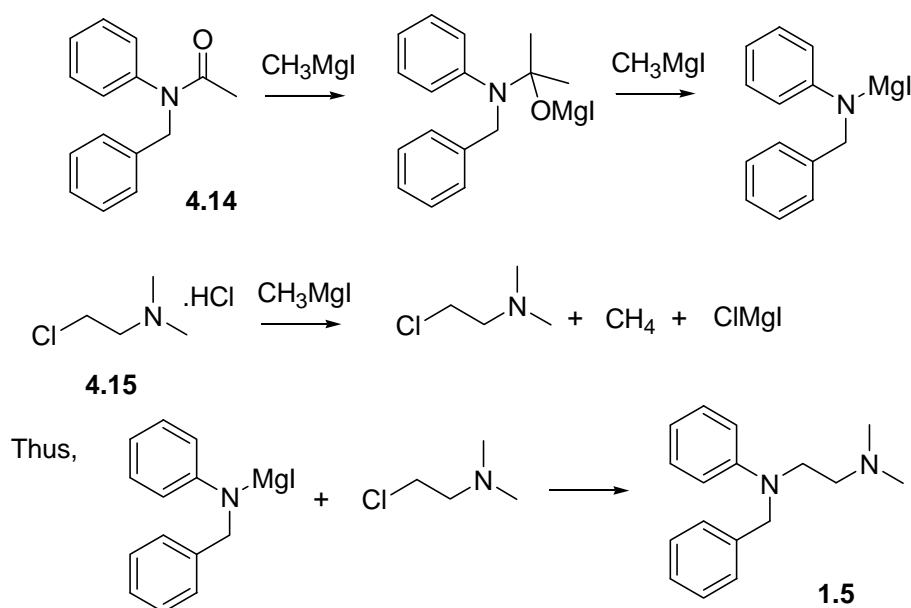
The ethylenediamines were the first group found to be clinically effective H<sub>1</sub>-antihistamines. Antergan **1.5** or phenbenzamine is considered as the first successful antihistamine tested in man in 1942<sup>[22]</sup> but was revised to Neo-Antergan **4.13** (or Pyrilamine maleate) in 1944<sup>[23]</sup> as it is found to be more potent and less toxic.<sup>20</sup> Tripeleennamine<sup>[24]</sup> **1.6** and Diphenhydramine<sup>[25]</sup> **4.12** were introduced in 1946 and are now still available over the counter.



**Figure 4.11** *Structures of Antergan and Neo-Antergan.*

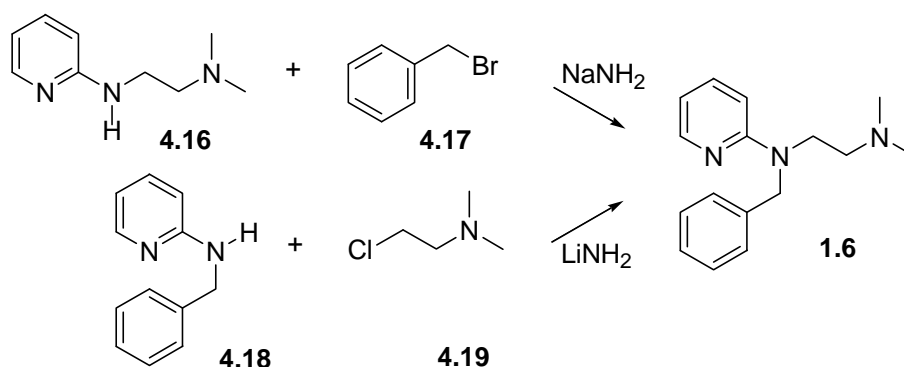
#### 4.4.1 Synthesis of Antergan and Tripeleennamine

The conventional synthesis of Antergan involves the treatment of *N*-benzyl-*N*-phenylacetamide **4.14** with an excess of methylmagnesium iodide followed by dimethylaminoethyl chloride hydrochloride **4.15**. The amount of the Grignard reagent used was enough to liberate the aminoalkyl halide from its salt. By this method, Antergan **1.5** was obtained in a moderate yield of 54% yield (Scheme 4.4).<sup>[26]</sup>



**Scheme 4.4** Conventional synthesis of Antergan.

Tripeleennamine **1.6** was first synthesised by Carl Djerassi working in the laboratory of Charles Hutterer at Ciba (Scheme 4.5). The patent describes the synthesis of Tripeleennamine **1.6** either by condensing 2-dimethylaminoethyl-aminopyridine **4.16** with 2 equiv. of benzyl bromide **4.17** in the presence of excess sodamide (72% yield) or condensing *N*-benzylaminopyridine **4.18** with dimethylaminoethyl chloride **4.19** in the presence of lithium amide (89% yield).<sup>[27]</sup> Tripeleennamine is marketed by Novartis under the trade name Pyribenzamine for the treatment of asthma, hayfever, rhinitis and urticaria but is less common due to the introduction of newer antihistamines.

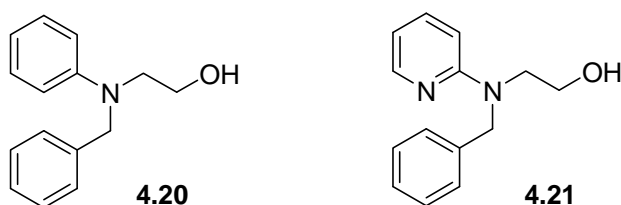


**Scheme 4.5** Conventional synthesis of Tripeleennamine.

In general, conventional syntheses of Antergan and Tripeleennamine also require the use of toxic alkyl halides and stoichiometric amounts of strong base are necessary for the *N*-alkylation reaction to proceed. Since the structure of Antergan has provided the framework of subsequent antihistamine agents, we wish to investigate the application of the ruthenium-catalysed synthesis of dimethylamines *via* “borrowing hydrogen” (Chapter 3.5) in the syntheses of Antergan **1.5** and Tripeleennamine **1.6**.

#### 4.4.2 Synthesis of Corresponding Alcohols of Antergan and Tripeleennamine by Conventional Methods and Borrowing Hydrogen Methodology

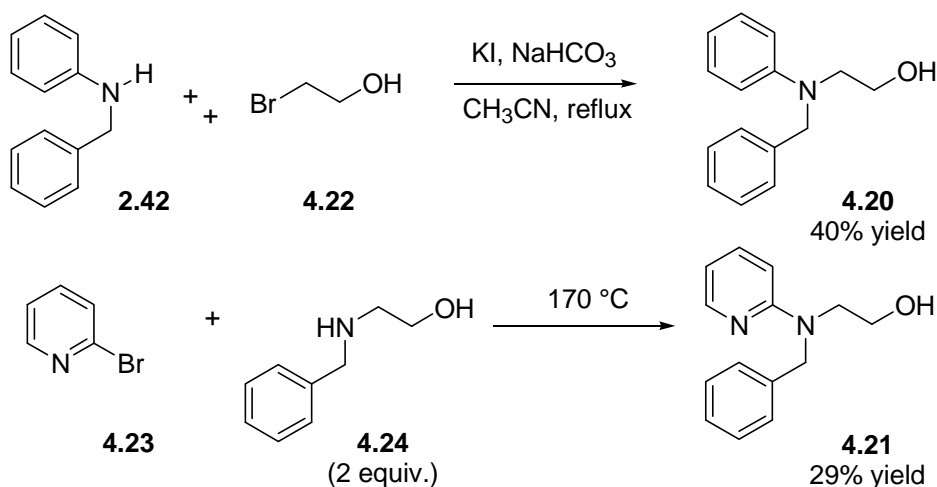
An examination of the structures of Antergan **1.5** and Tripeleennamine **1.6** reveals the presence of two tertiary amines and potentially, the “borrowing hydrogen” strategy can be applied in their syntheses. We began our investigation in the syntheses of Antergan and Tripeleennamine by considering the dimethylation of the corresponding alcohols **4.20** and **4.21** (Figure 4.12).



**Figure 4.12** Structures of the corresponding alcohols **4.20** and **4.21** of Antergan and Tripeleennamine.

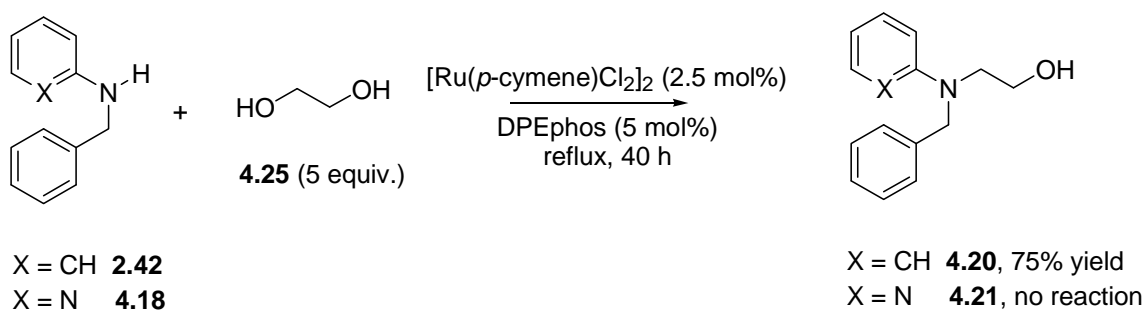
The starting alcohols were synthesised by conventional alkylation reactions with modest yields. *N*-Benzylaniline **2.42** was alkylated<sup>[28]</sup> with 2-bromoethanol **4.22** in the presence of NaHCO<sub>3</sub> to form compound **4.20** and *N*-benzylethanamine **4.24** was

alkylated<sup>[29]</sup> with 2-bromopyridine **4.23** by heating at 170 °C to form compound **4.21** (Scheme 4.6).



**Scheme 4.6** Synthesis of starting alcohols **4.20** and **4.21** by conventional alkylation reactions.

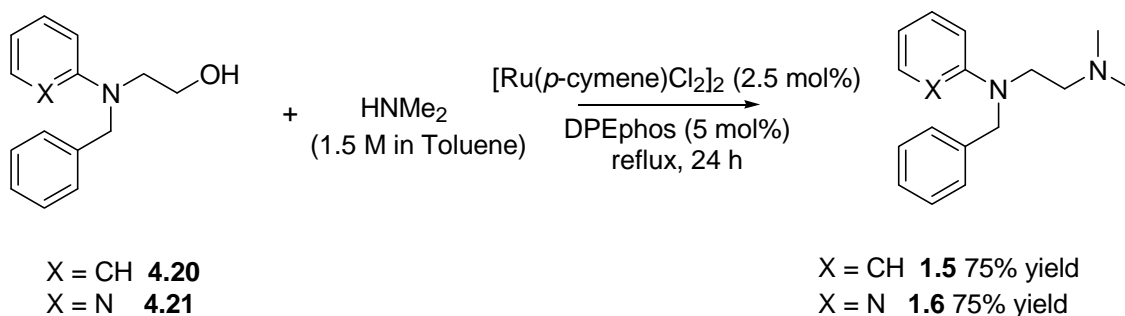
We next investigated the synthesis of the starting alcohols by the “borrowing hydrogen” methodology (Scheme 4.7). Our first attempt was to alkylate *N*-benzylaniline **2.42** with an excess of 1,2-ethanediol **4.25** (5 equiv.) at a catalyst loading of 2.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> in order to obtain alcohol **4.20**. An excess of the diol was used in order to minimise the amount of diamine which could be formed in the reaction and conversion of 84% of the crude product was observed after 24 hours. Encouraged by this observation we performed the same reaction at reflux for a longer period of 40 hours and we were pleased to find the crude NMR did not contain any starting material. The crude mixture was purified by column chromatography and an isolated yield of 70% of the desired product was obtained. The synthesis of starting alcohol **4.21** was attempted *via* the same strategy but no product was obtained.



**Scheme 4.7** Synthesis of starting alcohols **4.20** and **4.21** by “borrowing hydrogen” methodology.

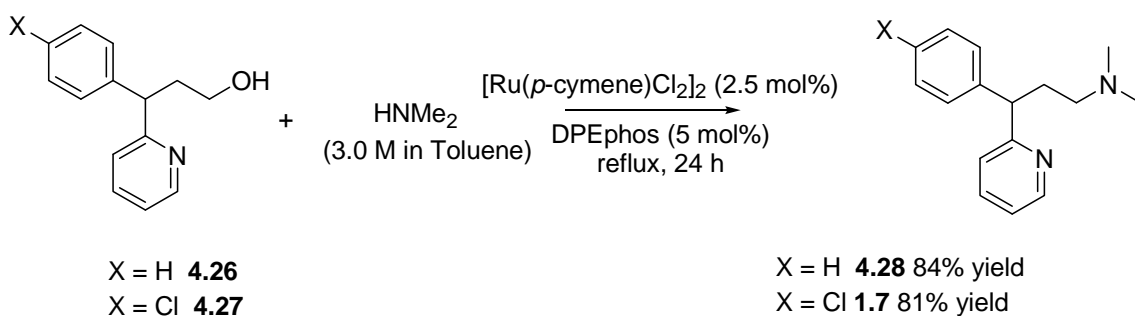
#### 4.4.3 Ruthenium-Catalysed Synthesis of Antergan and Tripelennamine by Borrowing Hydrogen

Having established a standard set of conditions in the synthesis of *N,N*-dimethylamines from alcohols (Chapter 3.5.2), we applied<sup>[30]</sup> the procedure to the synthesis of Antergan **1.5** and Tripelennamine **1.6** (Scheme 4.8). The reactions were performed with a slightly higher catalyst loading of 2.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> to obtain complete conversion into product (Scheme 4.6). However, the isolated yields obtained from these reactions were a moderate 75%. The reaction was performed using a lower catalyst loading of 0.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and we were pleased to find that a complete conversion into Tripelennamine **1.6** was observed. However, a lower conversion of 50% to product was obtained for Antergan **1.5** at a lower catalyst loading of 0.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>.



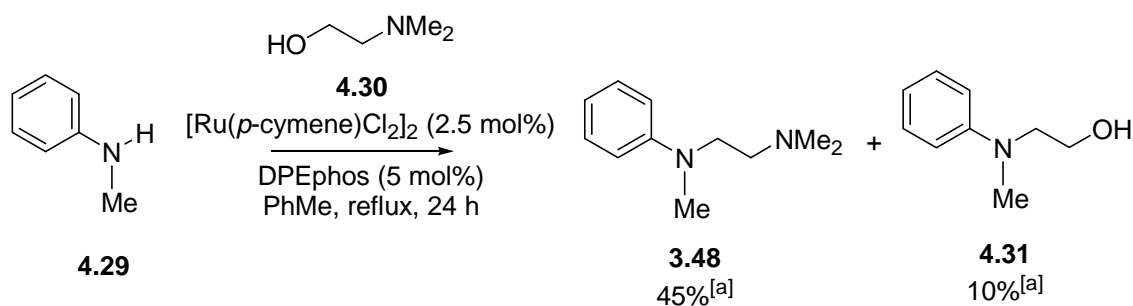
**Scheme 4.8** Ruthenium-catalysed synthesis of Antergan **1.5** and Tripeleennamine **1.6** by “borrowing hydrogen”.

Subsequently, in the course of a MChem research project,<sup>[31]</sup> it was shown that the “borrowing hydrogen” methodology could also be used in the synthesis of two other antihistamines namely, pheniramine **4.28** and chlorpheniramine **1.7** (commonly marketed as Piriton). The two antihistamines have similar structures with an all carbon backbone. Similarly, the reaction required a catalyst loading of 2.5 mol% [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> with DPEphos (Scheme 4.9) and both alcohol substrates (**4.26**, **4.27**) were synthesised by conventional methods.



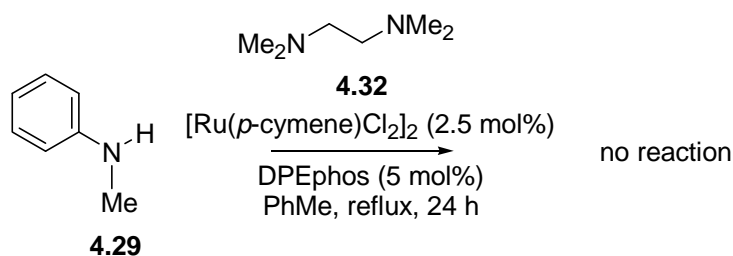
**Scheme 4.9** Ruthenium-catalysed synthesis of Pheniramine **4.24** and Chlorpheniramine **1.7** by “borrowing hydrogen”.

We also reasoned that an alternative approach to Antergan and Tripelennamine which are ethylenediamines could be carried out by the alkylation of the respective amine with *N,N*-dimethylaminoethanol **4.30** under the “borrowing hydrogen” methodology. We considered *N*-methylaniline **4.29** as our model reaction in this investigation. However, under the standard conditions, we discovered that the expected diamine product **3.48** was formed as well as the amino alcohol **4.31** as a significant by-product (Scheme 4.10).



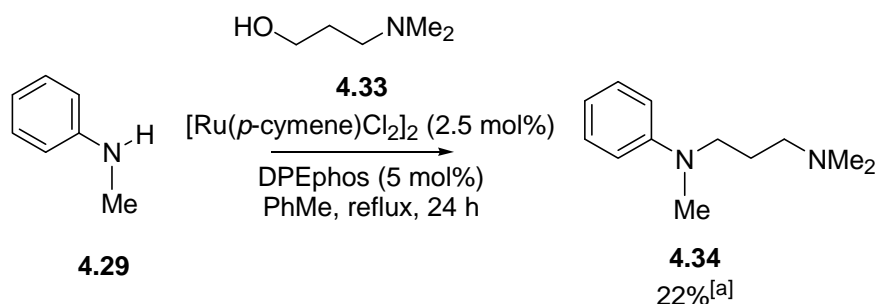
**Scheme 4.10** Alkylation of *N*-methylaniline **4.29** with *N,N*-dimethylaminoethanol **4.30** by “borrowing hydrogen” methodology. [a] Conversion determined by analysis of the  $^1\text{H}$  NMR spectrum.

This would suggest that there may have been oxidation of the amine as well as the alcohol (Scheme 4.10), but the reaction of **4.29** with tetramethylethylenediamine (TMEDA) **4.32** led to no product under these conditions showing that direct amine oxidation has not occurred (Scheme 4.11).



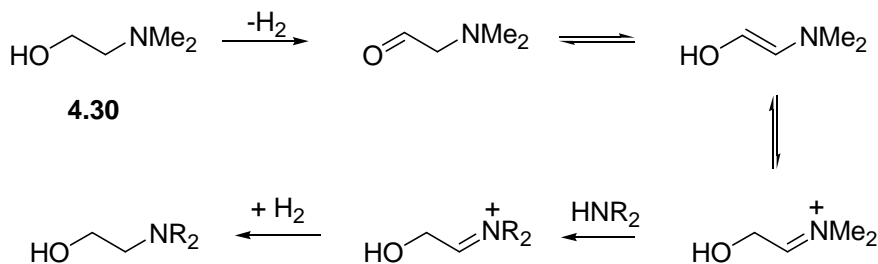
**Scheme 4.11** Attempted alkylation of *N*-methylaniline **4.29** with TMEDA **4.32** by “borrowing hydrogen” methodology.

Another alkylation reaction was carried out with amine **4.29** with dimethylaminopropanol **4.33** but the expected diamine product **4.34** with a low conversion and no amino alcohol side-product was obtained (Scheme 4.12). This implies that the extra carbon in **4.33** has stopped the transimination with the incoming amine (*vide infra*).



**Scheme 4.12** Attempted alkylation of *N*-methylaniline **4.29** with dimethylaminopropanol **4.34** by “borrowing hydrogen” methodology. [a] Conversion determined by analysis of the  $^1\text{H}$  NMR spectrum.

It was proposed that in the case of *N,N*-dimethylethanolamine **4.30** as an alkylating agent, the intermediate amino aldehyde is in equilibrium with a reactive iminium species which undergoes transimination with the incoming amine, prior to return of hydrogen to give the product, as shown in Scheme 4.13. This sequence accounts for amine exchange in an amino alcohol without a direct C-N oxidation step.



**Scheme 4.13** Proposed reactivity of *N,N*-dimethylethanolamine **4.30**.



## 4.5 Chapter Summary

The “borrowing hydrogen” methodology has been applied in the syntheses of the dopamine agonist Piribedil<sup>[18]</sup> and two antihistamines, Antergan and Tripeleennamine. A catalyst loading of 1.25 to 2.5 mol%  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  is required in order to obtain complete conversion into the desired product. In the course of finding an alternative approach to related structures involving the alkylation of an secondary amine with *N,N*-dimethylaminoethanol, it was discovered that as well as forming the expected diamine product, the amino alcohol was also formed as a significant by-product. We reasoned that a transimination reaction with an incoming amine has occurred in the reaction.

## 4.6 Conclusion and Future Directions

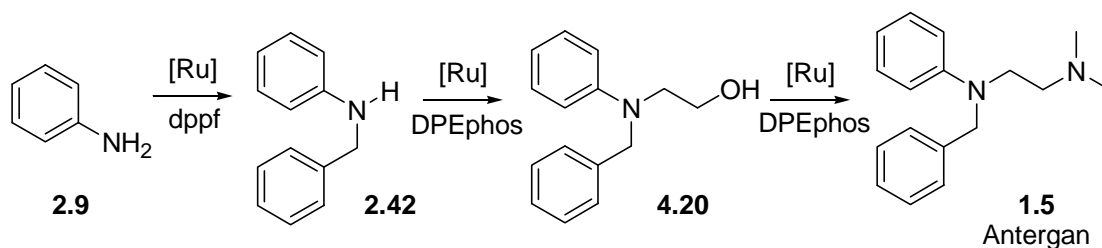
The  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}/\text{K}_2\text{CO}_3$  combination conditions were found to be highly efficient for the *N*-alkylation of primary amines with phenethyl alcohol by “borrowing hydrogen” particularly a simple amine such as *t*-butylamine. The use of anilines in alkylation reactions is usually unsuccessful but  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}/\text{K}_2\text{CO}_3$  combination conditions was also found to be successful in the synthesis of a range of *N*-phenylamines. Other amines such as enantiomerically pure (*R*)-(+)- $\alpha$ -methylbenzylamine afforded enantiomerically pure amine product as determined from the <sup>1</sup>H NMR spectrum in the presence of (*S*)-(+)-*O*-acetylmandelic acid. Subsequently, it was discovered that the addition of additives such as molecular sieves and base had no obvious beneficial effect on these reactions and were therefore omitted in our recent investigations. Hence, a number of primary alcohols and primary amines were converted into the corresponding secondary amines in good to excellent yields by simply heating a solution of the alcohol and amine at reflux in toluene in the presence of 2.5 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  and 5 mol% dppf for 24 hours.

During our attempt in the synthesis of primary amines by “borrowing hydrogen”, we discovered that the  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{dppf}$  combination is highly efficient for the *N*-alkylation of secondary amines with primary alcohols to form tertiary amines. This methodology has been applied to the one pot synthesis of Piribedil and other piperazine and morpholine-containing products whereby a lower catalyst loading of 1.25 mol% of  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  and 2.5 mol% dppf is sufficient for the transformation. We next applied this “borrowing hydrogen” strategy in the conversion of alcohols into *N,N*-dimethylamino compounds given the widespread occurrence of the dimethylamino

groups in pharmaceuticals. Dimethylamine was prepared as a solution in toluene by condensation of dimethylamine gas (b.p. 7 °C) and the exact concentration was determined by analysis of the integrals for the methyl peaks in the NMR spectrum. Optimisation of the reaction showed that ligands dppf and DPEphos were both effective in the reaction and DPEphos was used in subsequent reactions due to its cheaper cost. Dimethylamine was alkylated successfully with various alcohols and in the case of simple alcohols, the catalyst loading could be as low as 0.5 mol%  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (*i.e.* 1 mol% in Ru).

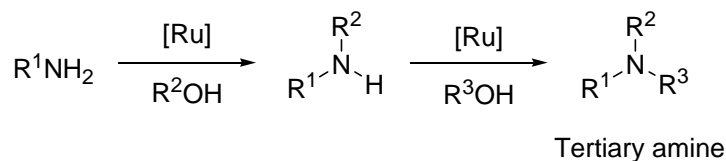
A plausible mechanism for the alkylation of an amine by alcohol using the  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ /diphosphine combination has been proposed. It is believed that *p*-cymene is dissociated in the active complex since *p*-cymene is also observed in the crude  $^1\text{H}$  NMR spectra at the end of the *N*-alkylation reactions. An alkoxy hydride complex is thought to be involved in the mechanism which can then undergo  $\beta$ -hydride transfer to form an aldehyde complex that subsequently dissociates an aldehyde. Imine formation and recomplexation leads to an imine complex, presumably by a dihydride complex. Finally,  $\beta$ -hydride transfer forms an amido complex and reductive elimination affords the amine product and the active ruthenium complex is regenerated. When the reaction involves the *N*-alkylation of a secondary amine, the intermediate iminium species would not be able to bind through the nitrogen, and the reaction could proceed either *via* a  $\eta^2$  iminium complex, or *via* the enamine.

The methodology is also successful in the syntheses of some antihistamine agents namely Antergan, Tripeleminamine, Pheniramine and Chlorpheniramine (commonly marketed as Piriton). A catalyst loading of 1.25 to 2.5 mol%  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  is required in order to obtain complete conversion into the desired product. It has been shown that Antergan can be synthesised from aniline using the “borrowing hydrogen” methodology that involves the synthesis of secondary amine **2.42** followed by the synthesis of tertiary amine **4.20** and in the last step involves the synthesis of Antergan **1.5** bearing a tertiary amine and a dimethylamino functional group (Scheme 4.14). All three steps have utilised the  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ /diphosphine combination which is relatively mild and good to excellent yields are obtained.



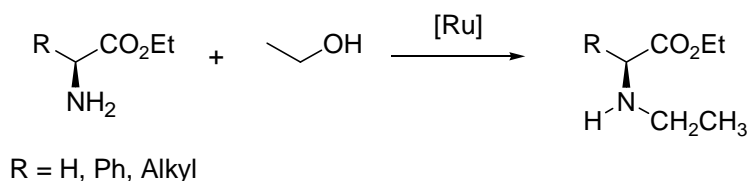
**Scheme 4.14** Synthesis of Antergan **1.5** by “borrowing hydrogen” methodology.

Hence, the methodology has a useful future application in the selective synthesis of a tertiary amine with three different substituents because the system is selective for the alkylation of primary amine and it is also selective for the alkylation of a secondary amine to give a tertiary amine. As described in Chapter 1, Yamaguchi and co-workers have described a sequential addition of two different alcohols to a primary amine leading to the formation of a tertiary amine with three different substituents using the  $[\text{Cp}^*\text{IrCl}_2]_2$  catalyst.<sup>[32]</sup> However, a similar strategy using a ruthenium catalyst has not been reported before and potentially the “borrowing hydrogen” methodology could be used in the syntheses of tertiary amines all in one pot (Scheme 4.15).



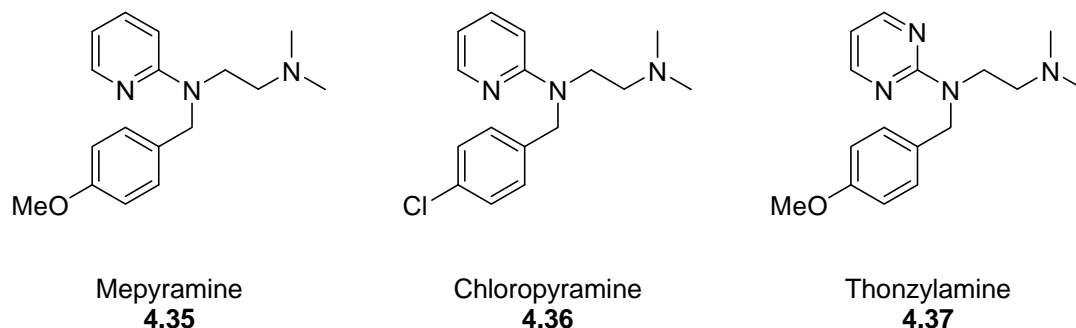
**Scheme 4.15** Synthesis of Antergan **1.5** by “borrowing hydrogen” methodology.

Another interesting future application of the “borrowing hydrogen” methodology is the *N*-alkylation of amino acid derivatives since mono-*N*-alkylated  $\alpha$ -amino acid derivatives are considered pharmacologically active compounds.<sup>[33]</sup> They are used as starting materials for the construction of peptidomimetics.<sup>[34]</sup> If this strategy shown in Scheme 4.16 is successful, the ester group of the *N*-alkylated mono-*N*-alkylated  $\alpha$ -amino acid derivatives in turn, can be hydrolysed to generate the biologically important mono-*N*-alkylated  $\alpha$ -amino acids. Otherwise, other derivatives of these mono-*N*-alkylated  $\alpha$ -amino acids could also be attempted.



**Scheme 4.16** Proposed *N*-alkylation of amino acid derivatives.

We have been successful in synthesising antihistamines and this chemistry could be applied in the synthesis of other drug molecules. Another future application of the “borrowing hydrogen” would be the syntheses of the antihistamines shown in Figure 4.13 that belongs to the substituted ethylene series of antihistamines.



**Figure 4.13** Structures of the antihistamines that belong to the substituted ethylene series.

Additionally, the “borrowing hydrogen” methodology is potentially attractive to pharmaceuticals and industry because: (i) a low loading of catalyst is needed in the reaction, (ii) no harmful and/or wasteful co-products (only H<sub>2</sub>O) are formed, (iii) alcohols are used instead which are more readily available than the potentially harmful alkyl halides or carbonyl compounds needed in other methods, (iv) equimolar amounts of starting materials used in the reaction means that all of the atoms of the reactants are incorporated. In conclusion, the methodology is a green, atom-efficient process which is in accordance to Trost’s atom economy principle.<sup>[35]</sup>

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## Chapter 5

### 5. Experimental

#### 5.1 General Experimental Methods

Reactions that require the use of anhydrous, inert atmosphere techniques were carried out under the atmosphere of nitrogen using Schlenk line techniques or use of Radley's or Young's tap carousel tubes. All solvents were distilled or obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system.

TLC was performed using plastic or aluminium backed plates precoated with Macherey-Nagel Sil G/UV<sub>254</sub> nm neutral silica was used to monitor reactions where appropriate. Visualisation of these plates was done by 254 nm UV light and/or KMnO<sub>4</sub> or ninhydrin dip followed by gentle warming. Organic layers were routinely dried with anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* using a Büchi rotary evaporator. Where necessary, further drying was obtained by exposure to high vacuum. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron) purchased from Fluorochem. In the case of isolation of secondary amine products, a few drops of aqueous ammonia were added to the eluting solvent mixture.

NMR spectra were run in CDCl<sub>3</sub> on either a Bruker Avance 250 (250 MHz), Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) or Bruker Avance 500 (500 MHz) instrument and recorded at the following frequencies: proton (<sup>1</sup>H – 250/300/500 MHz), carbon (<sup>13</sup>C – 62.9/75.5/125.8 MHz). Chemical shifts are reported relative to the residual solvent peak. Coupling constants (*J*) are recorded in Hz and multiplicities denoted as singlet (s), doublet (d), double to doublets (dd), double of doublet of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of triplets (tt), quartet (q), pentet (p), sextet, unresolved multiplet (m), broad (br.) or apparent (app.). Carbon-13 (δ <sup>13</sup>C) NMR spectra were also run in CDCl<sub>3</sub>. General assignments are classified as Ph (phenyl), Ar (aromatic), C (quaternary carbon), CH (methyne carbon), CH<sub>2</sub> (methylene carbon) and CH<sub>3</sub> (methyl carbon). Structural assignment of both protons and carbons were achieved with comparisons from analogous literature compounds where possible. Protons that possess chemical but not magnetic equivalence (AA'BB' systems) as in the

case of 1,4-disubstituted aromatics are reported as multiplets or doublets, depending on their appearance in spectra.

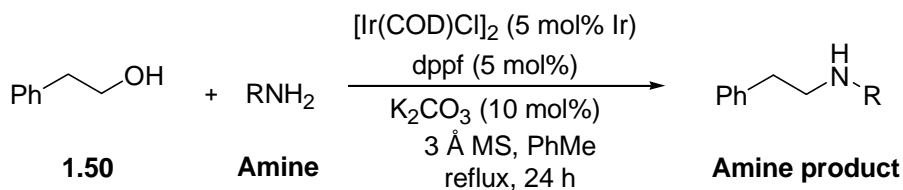
Optical rotation was recorded on Optical Activity, AA-10 Automatic polarimeter. Melting points were carried out on a Gallenkamp MF-370 hot stage melting point apparatus and are uncorrected.

A micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10  $\mu$ L of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10  $\mu$ L of a calibrant of 5 mM sodium formate was injected before the sample. The observed mass and isotope pattern perfectly matched the corresponding theoretical values as calculated from the expected elemental formula.

Unless preparative details are provided, all chemicals were commercially available and purchased from either Acros organics, Aldrich, Alfa Aesar, Avocado, Fluka, Fluorochem, Lancaster or Strem chemical companies.

## 5.2 Experimental Procedures for Chapter 2

### 5.2.1 General Procedure I for the Iridium-catalysed *N*-Alkylation of Amines with Phenethyl Alcohol as Summarised in Table 2.1

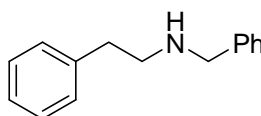


[Ir(COD)Cl]<sub>2</sub> (16.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (6.4 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a pressure tube and the mixture was exposed to nitrogen for 10 minutes. Amine (1 mmol), phenethyl alcohol (119  $\mu$ L, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The resulting orange-brown mixture was quenched with diethyl ether (10 mL) and poured into water (50 mL) and diethyl ether



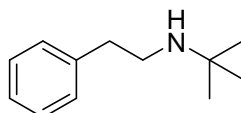
(50 mL). The ethereal layer was separated and the aqueous layer was further extracted with diethyl layer ( $3 \times 50$  mL). The combined organic extracts were washed with saturated brine (50 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford a brown crude mixture.

*N*-Benzyl-2-phenethylamine<sup>[1]</sup> **1.51** (Entry 1, Table 2.1)



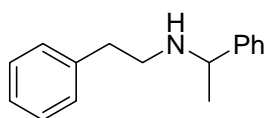
Following **general procedure I** using benzyl amine (109  $\mu\text{L}$ , 1 mmol), the product was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60  $^{\circ}\text{C}$ )/dichloromethane/ethyl acetate (2:1:1),  $R_f = 0.16$ , to give the title compound **1.51** as a brown liquid (0.15 g, 72% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  7.32–7.16 (10H, m, ArH), 3.79 (2H, s,  $\text{NHCH}_2\text{Ph}$ ), 2.92–2.79 (4H, m,  $\text{NHCH}_2\text{CH}_2\text{Ph}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  140.23 (C), 140.02 (C), 128.72 (CH), 128.44 (CH), 128.38 (CH), 128.08 (CH), 126.90 (CH), 126.13 (CH), 53.85 ( $\text{CH}_2$ ), 50.53 ( $\text{CH}_2$ ), 36.35 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{15}\text{H}_{17}\text{N}$   $[\text{M}+\text{H}]^+$ : 212.1439. Found: 212.1416.

*tert*-Butyl(2-phenylethyl)amine<sup>[2]</sup> **2.12** (Entry 3, Table 2.1)



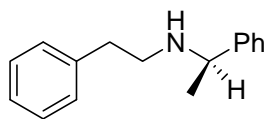
Following **general procedure I** using *t*-butylamine (105  $\mu\text{L}$ , 1 mmol), the product was obtained and purified by column chromatography eluting with diethyl ether,  $R_f = 0.05$ , to give the title compound **2.12** as a pale brown liquid (62.1 mg, 52% conversion, 35% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  7.36–7.22 (5H, m, ArH), 2.91–2.80 (4H, m,  $\text{PhCH}_2\text{CH}_2\text{NH}$ ), 1.12 (9H, s,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  140.2 (C), 128.7 (CH), 128.4 (CH), 50.3 (C), 44.1 ( $\text{CH}_2$ ), 37.2 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{12}\text{H}_{20}\text{N}$   $[\text{M}+\text{H}]^+$ : 178.1596. Found: 178.1588.

(±)-Phenethyl-(1-phenylethyl)amine<sup>[3]</sup> **2.14** (Entry 4, Table 2.1)



Following **general procedure I** using (±)-α-methylbenzylamine (129 μL, 1 mmol), the product was purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (3:2),  $R_f = 0.23$ , to give the title compound **2.14** as a pale brown liquid (46.2 mg, 52% conversion, 21% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.34-7.15 (10H, m, ArH), 3.79 (1H, q,  $J = 6.6$  Hz, CHCH<sub>3</sub>), 2.83-2.68 (4H, m, PhCH<sub>2</sub>CH<sub>2</sub>NH), 1.34 (3H, d,  $J = 6.6$  Hz, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  140.0 (C), 128.7 (C), 128.42 (CH), 128.39 (CH), 126.9 (CH), 126.6 (CH), 126.1 (CH), 58.2 (CH), 48.9 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 24.2 (CH<sub>3</sub>). ESI-MS: Calculated for  $\text{C}_{16}\text{H}_{20}\text{N}$   $[\text{M}+\text{H}]^+$ : 226.1596. Found: 226.1586.

(*R*)-α-Phenethyl-(1-phenylethyl)amine<sup>[3]</sup> **2.16** (Entry 5, Table 2.1)

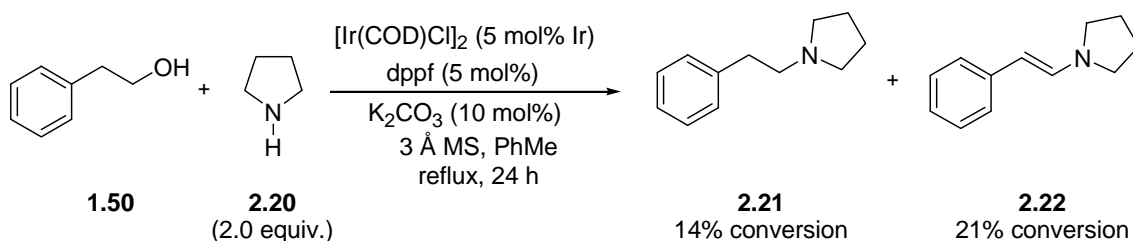


Following **general procedure I** using (*R*)-(+)-α-Methylbenzylamine (129 μL, 1 mmol), the product was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (3:2),  $R_f = 0.18$ , to give the title compound **2.16** as a yellowish-brown liquid (75.1 mg, 59% conversion, 33% yield, ee = 94%),  $[\alpha]_D^{25} +54.2$  ( $c$  2.84,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.34-7.15 (10H, m, ArH), 3.78 (1H, q,  $J = 6.6$  Hz, CHCH<sub>3</sub>), 2.82-2.67 (4H, m, PhCH<sub>2</sub>CH<sub>2</sub>NH), 1.34 (3H, d,  $J = 6.6$  Hz, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  140.0 (C), 128.7 (C), 128.41 (CH), 128.39 (CH), 126.9 (CH), 126.5 (CH), 126.1 (CH), 58.2 (CH), 48.9 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 24.2 (CH<sub>3</sub>). ESI-MS: Calculated for  $\text{C}_{16}\text{H}_{20}\text{N}$   $[\text{M}+\text{H}]^+$ : 226.1596. Found: 226.1578.

Enantiomeric resolution<sup>[4]</sup> was achieved *via* salt formation with (*S*)-(+)-O-acetylmandelic acid: (*R*)-α-Phenethyl-(1-phenylethyl)amine (0.0101 g, 0.0448 mmol) and (*S*)-(+)-O-acetylmandelic acid (0.0172 g, 0.089 mmol) were dissolved in  $\text{CDCl}_3$  (0.6 mL). Analysis of the  $^1\text{H}$  NMR (250 MHz, 25 °C) spectrum shows a quartet at

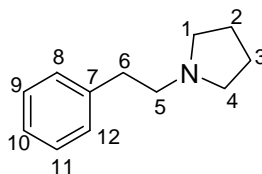
δ3.97 allowing a rough integration of 33.33:1.01 for the enantiomers. The ee was calculated and found to be 94%.

### 5.2.2 Preparation of 1-Phenethylpyrrolidine **2.21** and 1-Styrylpyrrolidine **2.22** (Scheme 2.8)

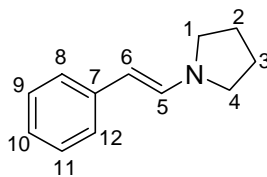


$[\text{Ir}(\text{COD})\text{Cl}]_2$  (16.8 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (6.9 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a pressure tube and the mixture was exposed to nitrogen for 10 minutes. Pyrrolidine (167  $\mu\text{L}$ , 2 mmol), phenethyl alcohol (119  $\mu\text{L}$ , 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was quenched with diethyl ether (10 mL) and poured into water (50 mL) and diethyl ether (50 mL). The ethereal layer was separated and the aqueous layer was further extracted with diethyl ether (3  $\times$  50 mL). The combined organic extracts were washed with saturated brine (50 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford a brownish crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (**2.21** at 14% conversion, **2.22** at 21% conversion):

#### 1-Phenethylpyrrolidine **2.21**

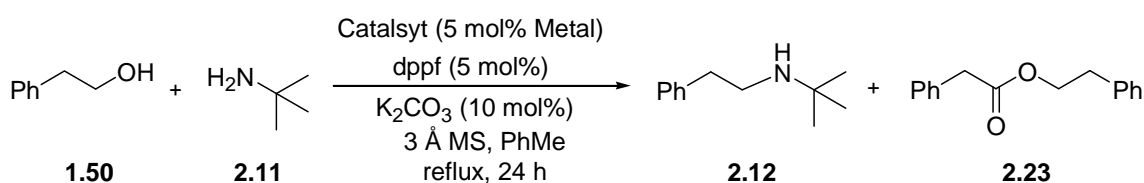


$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.28-7.06 (5H, m, ArH), 2.82-2.60 (4H, m,  $\text{H}_5$ ,  $\text{H}_6$ ), 2.54-2.49 (4H, m,  $\text{H}_1$ ,  $\text{H}_4$ ), 1.72-1.79 (4H, m,  $\text{H}_2$ ,  $\text{H}_3$ ). This is consistent with literature data.<sup>[5]</sup>

1-Styrylpyrrolidine **2.22**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.28-7.06 (5H, m, ArH), 6.98 (1H, d,  $J = 13.8$  Hz, H<sub>5</sub>), 5.02 (1H, d,  $J = 13.8$  Hz, H<sub>6</sub>), 3.17-3.13 (4H, m, H<sub>1</sub>, H<sub>4</sub>), 1.86-1.82 (4H, m, H<sub>2</sub>, H<sub>3</sub>). This is consistent with literature data.<sup>[6]</sup>

### 5.2.3 General Procedure II for the Preparation of *tert*-Butyl(2-phenylethyl)amine **2.12**



$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol) (note: 2.5 mol% dimer is 5 mol% Ru), dppe (27.7 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. *t*-Butylamine (105  $\mu\text{L}$ , 1 mmol), phenethyl alcohol (119  $\mu\text{L}$ , 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Reaction conversion was determined by analysis of the peak integral ratios characteristic of phenethyl alcohol **1.50**, amine product **2.12** and ester **2.23** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

#### Variation of Catalyst

Following **general procedure II**,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  was exchanged for various catalysts as described in Table 2.2, Section 2.4.

#### Variation of Ligand

Following **general procedure II**, dppe was exchanged for alternative ligands as described in Table 2.3, Section 2.4. For the monophosphine ligands, 2 equivalents of

the ligand were used. For example, for Entry 7, Table 2.3, the reaction was carried out in the presence of:  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol),  $\text{PPh}_3$  (26.2 mg, 0.10 mmol) and  $\text{K}_2\text{CO}_3$  (13.8 mg, 0.1 mmol).

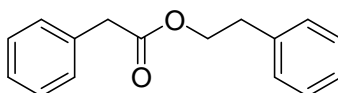
### Variation of Base

Following **general procedure II**,  $\text{K}_2\text{CO}_3$  was exchanged for various bases as described in Table 2.4, Section 2.4.

### Variation of Alcohol:Amine ratio

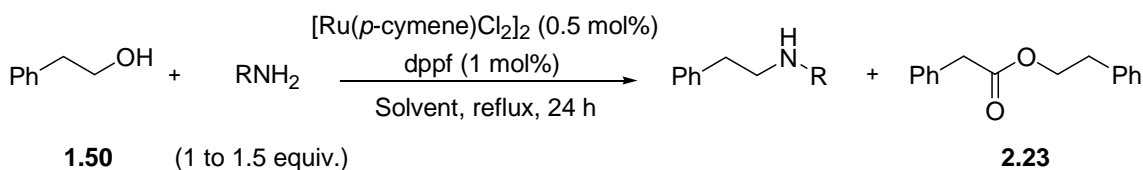
Following **general procedure II**, the reactions were carried out according to the alcohol:amine ratio as described in Table 2.5, Section 2.4.

## 5.2.4 Procedure for the Attempted Preparation of 2-Phenylethyl Phenylacetate 2.23 (Scheme 2.10)



$\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Phenethyl alcohol (119  $\mu\text{L}$ , 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a brownish-black crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (62% conversion).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.40-7.14 (10H, m, ArH), 4.33 (2H, t,  $J = 7.0$  Hz,  $\text{PhCH}_2\text{CH}_2$ ), 3.62 (2H, s,  $\text{PhCH}_2\text{CO}_2$ ), 2.93 (2H, t,  $J = 6.9$  Hz,  $\text{PhCH}_2\text{CH}_2$ ). This is consistent with literature data.<sup>[7]</sup>

## 5.2.5 General Procedure III for the Preparation of Secondary Amines as Summarised in Table 2.6



[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (7.7 mg, 0.0125 mmol), dppf (13.9 mg, 0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. *t*-Butylamine (264 µL, 2.5 mmol), phenethyl alcohol (299 µL, 2.5 mmol) and anhydrous toluene (2.5 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Reaction conversion was determined by analysis of the peak integral ratios characteristic of phenethyl alcohol **1.50**, amine product **2.12** and ester **2.23** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

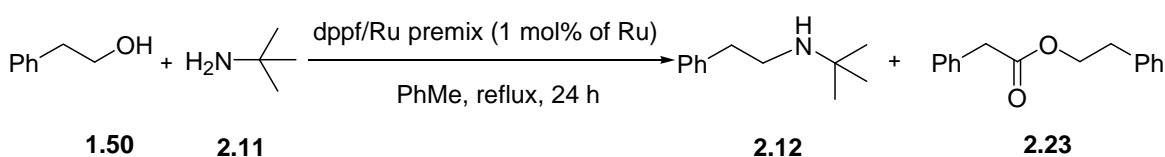
### Variation of Alcohol:Amine ratio

Following **general procedure III**, the reactions were carried out according to the alcohol: amine ratio as described in Table 2.6, Section 2.4.

### Variation of Amines

Following **general procedure III**, *t*-butylamine was exchanged with two other amines as described in Table 2.6, Section 2.4.

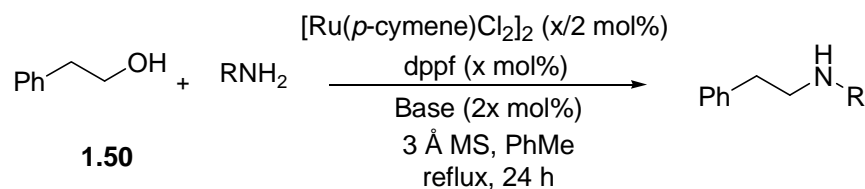
#### 5.2.6 Procedure for the Preparation of *tert*-Butyl(2-phenylethyl)amine **2.12** Using dppf/Ru Premix as Summarised in Table 2.6



[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (7.7 mg, 0.0125 mmol), dppf (13.9 mg, 0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (6.9 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Anhydrous toluene (2.5 mL) was added dropwise and the reaction mixture was heated to reflux for 1 hour. *t*-Butylamine (264 µL, 2.5 mmol) and phenethyl alcohol (299 µL, 2.5 mmol) were then added dropwise to the refluxing mixture and further heated for 24 hours. The resulting mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown

crude mixture. Reaction conversion was determined by analysis of the peak integral ratios characteristic of phenethyl alcohol **1.50**, amine product **2.12** and ester **2.23** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### 5.2.7 General Procedure IV for the Preparation of Secondary Amines by Varying Catalyst Loading as Summarised in Table 2.7



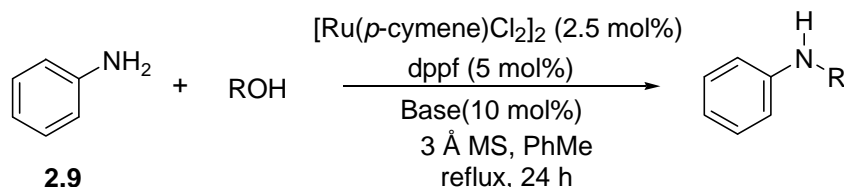
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (9.2 mg, 0.015 mmol) (*i.e.* 3 mol% Ru), dppf (16.6 mg, 0.03 mmol),  $\text{K}_2\text{CO}_3$  (8.3 mg, 0.06 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Amine (1.0 mmol), phenethyl alcohol (119  $\mu\text{L}$ , 1.0 mmol) and anhydrous toluene (1.0 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen for 10 minutes at room temperature before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a dark brown crude mixture.

*N*-(2-Phenethyl)aniline **2.10**: Following **general procedure IV**, aniline (91  $\mu\text{L}$ , 1 mmol) was used in the reaction. Catalyst loading were varied at 4 mol% of Ru {12.2 mg, 0.020 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } and 5 mol% of Ru {15.3 mg, 0.025 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } as described in Table 2.7, in Section 2.4. Reaction conversion was determined by analysis of the peak integral ratios characteristic of phenethyl alcohol **1.50**, amine product **2.10** and ester **2.23** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

( $\pm$ )-Phenethyl-(1-phenylethyl)amine **2.14**: Following **general procedure IV**, ( $\pm$ )- $\alpha$ -methylbenzylamine (129  $\mu\text{L}$ , 1 mmol) was used in the reaction. Catalyst loading were varied at 4 mol% of Ru {12.2 mg, 0.020 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } and 5 mol% of Ru {15.3 mg, 0.025 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } as described in Table 2.7, in Section 2.4. Reaction conversion was determined by analysis of the peak integral ratios

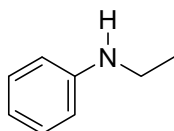
characteristic of phenethyl alcohol **1.50**, amine product **2.14**, ester **2.23** and imine **2.24** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### 5.2.8 General Procedure V for the *N*-Alkylation of Aniline by Simple Alcohols with base (Scheme 2.13 and Scheme 2.15)



$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (16.8 mg, 0.027 mmol), dppe (30.4 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (15.2 mg, 0.11 mmol) and activated molecular sieves (0.52, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aniline (0.1 mL, 1.1 mmol), alcohol and anhydrous toluene (1.0 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a red-black crude mixture.

#### *N*-Ethylaniline<sup>[8]</sup> **2.35**

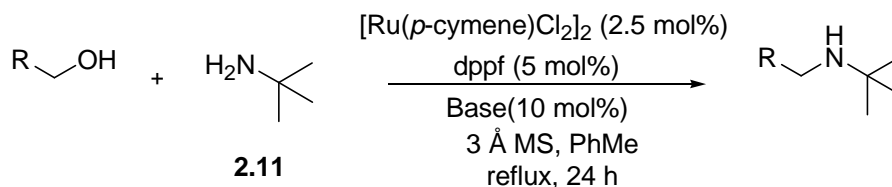


Following **general procedure V** using absolute ethanol (0.31 mL, 4.8 equiv., 5.28 mmol), the product was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/diethyl ether (19:1),  $R_f = 0.20$ , to give the title compound **2.35** as a colourless liquid (0.13 g, 96% conversion, 85% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.14 (2H, m, ArH), 6.64 (1H, tt,  $J = 7.3, 0.9$  Hz, ArH), 6.54 (2H, m, ArH), 3.50 (br. s, NH), 3.09 (2H, q,  $J = 7.1$  Hz,  $\text{CH}_2$ ), 1.18 (3H, t,  $J = 7.1$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  148.63 (C), 129.64 (CH), 117.83 (CH), 113.33 (CH), 39.03 ( $\text{CH}_2$ ), 15.23 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_8\text{H}_{12}\text{N}$   $[\text{M}+\text{H}]^+$ : 122.0970. Found: 122.0964.



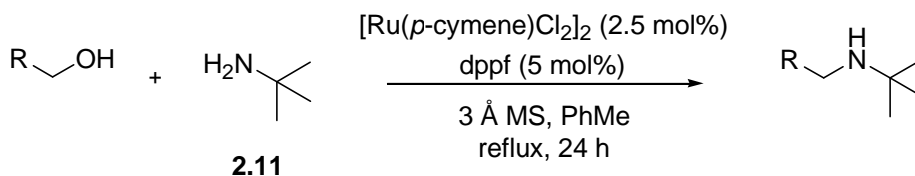
### 5.2.9 General Procedure VI for the *N*-Alkylation of *t*-Butylamine 2.11 with Primary Alcohols Summarised in Table 2.8

**With Base:**



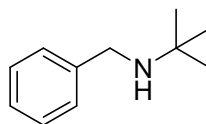
[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppe (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. *t*-Butylamine (105 µL, 1 mmol), alcohol and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo*. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum. The crude product was purified by column chromatography on silica gel where necessary.

**Without Base and 3 Å MS:**



[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol) and dppe (27.7 mg, 0.05 mmol) were added to a Young's tap carousel tube and the mixture was exposed to nitrogen for 10 minutes. *t*-Butylamine (105 µL, 1 mmol), alcohol and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and the solvents were concentrated *in vacuo*. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum. The crude product was purified by column chromatography on silica gel where necessary.

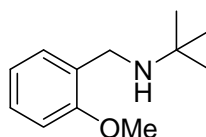
*N*-(*tert*-Butyl)benzylamine<sup>[9]</sup> **2.27** (Entry 1, Table 2.8)



Following **general procedure VI with base**, benzyl alcohol (103  $\mu$ L, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a brownish-black crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (84% conversion).

Following **general procedure VI without base**, benzyl alcohol (103  $\mu$ L, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brownish-black crude mixture and the product was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.19$ , to give the title compound **2.27** as a pale yellow liquid (0.10 g, 62% conversion, 60% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.35-7.21 (5H, m, ArH), 3.72 (2H, s,  $\text{PhCH}_2$ ), 1.17 (9H, s,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  141.2 (C), 128.4 (CH), 128.3 (CH), 126.76 (CH), 50.8 (C), 47.2 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{11}\text{H}_{18}\text{N}$   $[\text{M}+\text{H}]^+$ : 164.1439. Found: 164.1439.

*tert*-Butyl-(2-methoxybenzyl)amine **2.29** (Entry 2, Table 2.8)

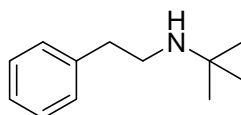


Following **general procedure VI with base**, 2-methoxy benzyl alcohol (133  $\mu$ L, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a brown crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (73% conversion).

Following **general procedure VI without base**, 2-methoxy benzyl alcohol (133  $\mu$ L, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brownish-black crude mixture and the product was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.24$ , to give the title compound **2.29** as a pale yellow liquid (0.11g, 87% conversion, 68% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.33-7.22 (2H, m, ArH), 6.92 (1H, t,  $J = 6.5$  Hz, ArH), 6.85 (1H, d,  $J = 8.1$  Hz, ArH), 3.85 (3H, s,  $\text{OCH}_3$ ), 3.74 (2H, s,  $\text{PhCH}_2$ ), 1.20

(9H, s, C(CH<sub>3</sub>)<sub>3</sub>). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C): δ 157.50 (C), 129.94 (CH), 128.82 (C), 128.11 (CH), 120.62 (C), 110.23 (CH), 55.22 (CH<sub>3</sub>), 51.06 (C), 42.43 (CH<sub>2</sub>), 28.86 (CH<sub>3</sub>). IR (neat): 3435, 2965, 2836, 1641, 1603, 1590, 1464, 1362, 1243, 1176, 1119, 1032, 753. ESI-MS: Calculated for C<sub>12</sub>H<sub>20</sub>NO [M+H]<sup>+</sup>: 194.1545. Found: 194.1539.

*tert*-Butyl(2-phenylethyl)amine<sup>[2]</sup> **2.12** (Entry 3, Table 2.8)

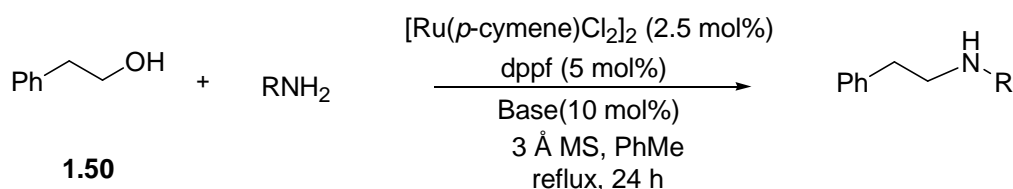


Following **general procedure VI with base**, 2-phenethyl alcohol (119 μL, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Purification by column chromatography eluting with diethyl ether, R<sub>f</sub> = 0.09 gave the title compound **2.12** as a yellow liquid (0.16 g, 96% conversion, 88% yield). The spectroscopy data was consistent with the analytical data reported previously (Entry 3, Table 2.1).

Following **general procedure VI without base**, 2-phenethyl alcohol (119 μL, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brownish-black crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (94% conversion).

### 5.2.10 General Procedure VII for the *N*-Alkylation of Primary Amines with Phenethyl Alcohol 1.50 as Summarised in Table 2.9

**With base:**



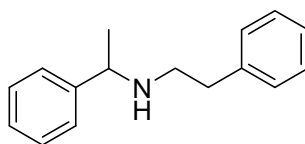
[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Amine, phenethyl alcohol (119 μL, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction

mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum.

**Without base and 3 Å MS:**

[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol) and dppf (27.7 mg, 0.05 mmol) were added to a Young's tap carousel tube and the mixture was exposed to nitrogen for 10 minutes. Amine, phenethyl alcohol (119 μL, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and the solvents were concentrated *in vacuo*. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum. The crude product was purified by column chromatography on silica gel where necessary.

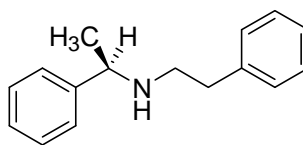
(±)-Phenethyl-(1-phenylethyl)amine<sup>[3]</sup> **2.14** (Entry 1, Table 2.9)



Following **general procedure VII with base**, (±)-α-methylbenzylamine (127 μL, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. The products were isolated by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (3:2). Product was isolated as a yellow liquid (0.21 g, 100% conversion, 93% yield). The spectroscopy data was consistent with the analytical data reported previously (Entry 4, Table 2.1).

Following **general procedure VII without base**, (±)-α-methylbenzylamine (127 μL, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brownish-black crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (100% conversion).

(*R*)- $\alpha$ -Phenethyl-(1-phenylethyl)amine<sup>[3]</sup> **2.16** (Entry 2, Table 2.9)

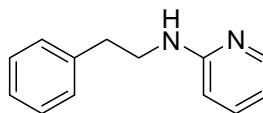


Following **general procedure VII with base**, (*R*)-(+)- $\alpha$ -Methylbenzylamine (127  $\mu$ L, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Product was isolated as a yellow liquid (0.16 g, 100% conversion, 70% yield). The spectroscopy data was consistent with the analytical data reported previously (Entry 5, Table 2.1).

Enantiomeric resolution<sup>[4]</sup> was achieved *via* 1:1 salt formation with (*S*)-(+)-*O*-acetylmandelic acid: (*R*)- $\alpha$ -Phenethyl-(1-phenylethyl)amine (0.0101 g, 0.0448 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (0.0087 g, 0.0448 mmol) were dissolved in CDCl<sub>3</sub> (0.6 mL). Analysis of the <sup>1</sup>H NMR (250 MHz, 25 °C) spectrum shows a quartet at  $\delta$ 4.00 allowing a rough integration of 1.000:0.022 for enantiomers (see Appendix A). Since the original spectrum was difficult to resolve, we irradiated at  $\delta$ 1.55 to give 2 singlets at an integration of 1.000:0.016 from which the ee was calculated and found to be 97%.

Following **general procedure VII without base**, (*R*)-(+)- $\alpha$ -Methylbenzylamine (127  $\mu$ L, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (100% conversion).

2-Phenylethylaminopyridine<sup>[10]</sup> **2.31** (Entry 3, Table 2.9)



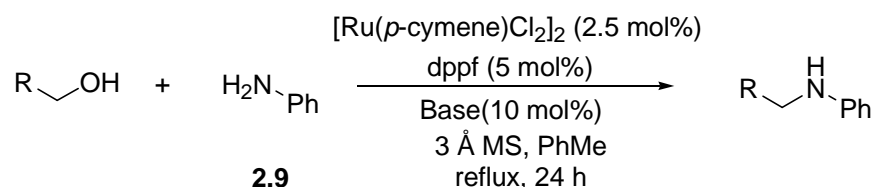
Following **general procedure VII with base**, 2-aminopyridine (94.1 mg, 1 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a brownish-black crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (69% conversion).

Following **general procedure VII without base**, 2-aminopyridine (94.1 mg, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brownish-black crude mixture and the product was obtained and purified by column

chromatography eluting with dichloromethane/methanol (99:1),  $R_f = 0.31$ , to give the title compound **2.31** as a pale brown liquid (0.16 g, 93% conversion, 78% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  8.07 (1H, dd,  $J = 5.0, 1.1$  Hz, py), 7.42-7.30 (1H, m, py), 7.29-7.18 (5H, m, ArH), 6.55 (1H, ddd,  $J = 7.1$  Hz, 5.0, 0.9 Hz, py), 6.35 (1H, app. d,  $J = 8.4$  Hz, py), 4.52 (1H, br. s, NH), 3.54 (2H, app. q,  $J = 6.9$  Hz,  $\text{CH}_2\text{NH}$ ), 2.91 (2H, d,  $\text{PhCH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  158.5 (C), 148.1 (CH), 139.2 (C), 137.4 (CH), 128.8 (CH), 128.6 (CH), 126.4 (CH), 112.9 (CH), 106.8 (CH), 43.3 ( $\text{CH}_2$ ), 35.7 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{13}\text{H}_{14}\text{N}_2$   $[\text{M}+\text{H}]^+$ : 199.1235. Found: 199.1230.

### 5.2.11 General Procedure VIII for the *N*-Alkylation of Aniline with Different Primary Alcohols as Summarised in Table 2.10

**With Base:**



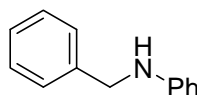
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aniline (91  $\mu\text{L}$ , 1 mmol), alcohol (1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite® and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture.

**Without Base and 3 Å MS:**

$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol) and dppf (27.7 mg, 0.05 mmol) were added to a Young's tap carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aniline (91  $\mu\text{L}$ , 1 mmol), alcohol (1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and the

solvents were concentrated *in vacuo*. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum. The crude product was purified by column chromatography on silica gel where necessary.

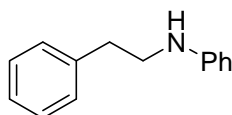
*N*-Benzylaniline<sup>[11]</sup> **2.42** (Entry 1, Table 2.10)



Following **general procedure VIII with base**, benzyl alcohol (103  $\mu\text{L}$ , 1 mmol) was used in the reaction. The product was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/ethyl acetate (20:1),  $R_f = 0.24$  to give the title compound **2.42** as a pale yellow liquid (0.15 g, 100% conversion, 80% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  7.41-7.17 (7H, m, ArH), 6.76-6.71 (1H, m, ArH), 6.67-6.64 (2H, m, ArH), 4.34 (2H, s,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}\text{C}$ ):  $\delta$  148.0 (C), 139.3 (C), 129.2 (CH), 128.6 (CH), 127.5 (CH), 127.2 (CH), 117.6 (CH), 112.8 (CH), 48.3 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{13}\text{H}_{14}\text{N}$   $[\text{M}+\text{H}]^+$ : 184.1126. Found: 184.1124.

Following **general procedure VIII without base**, benzyl alcohol (103  $\mu\text{L}$ , 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (95% conversion).

*N*-(2-Phenylethyl)aniline<sup>[12]</sup> **2.10** (Entry 2, Table 2.10)

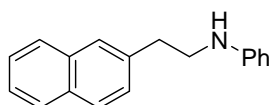


Following **general procedure VIII with base**, phenethyl alcohol (119  $\mu\text{L}$ , 1 mmol) was used. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (94% conversion).

Following **general procedure VIII without base**, 2-phenethyl alcohol (119  $\mu\text{L}$ , 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture and the product was obtained and purified by column chromatography eluting with hexane/ethyl acetate (20:1),  $R_f = 0.18$ , to give the title

compound **2.10** as a colourless liquid (0.17 g, 100% conversion, 84% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.86-7.80 (3H, m, ArH), 7.69 (1H, s, ArH), 7.52-7.18 (5H, m, ArH), 6.76 (1H, app. t,  $J = 7.3$  Hz, ArH), 6.66 (2H, d,  $J = 7.7$  Hz, ArH), 3.52 (2H, t,  $J = 7.1$  Hz,  $\text{CH}_2\text{NH}$ ), 3.12 (2H, t,  $J = 7.1$  Hz,  $\text{PhCH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  147.9 (C), 139.3 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 126.4 (CH), 117.6 (CH), 113.1 (CH), 45.1 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{14}\text{H}_{16}\text{N}$   $[\text{M}+\text{H}]^+$ : 198.1283. Found: 198.1273.

*N*-(2-(2-Naphthyl)ethyl)aniline<sup>[13]</sup> **2.44** (Entry 3, Table 2.10)

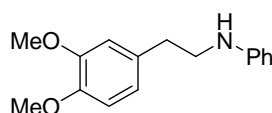


Following **general procedure VIII with base**, 2-naphthalene ethanol (0.17 g, 1 mmol) was used in the reaction. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (100% conversion).

Following **general procedure VIII without base**, 2-naphthalene ethanol (0.17 g, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture and the product obtained was purified by column chromatography eluting with hexane/ethyl acetate (20:1),  $R_f = 0.18$ , to give the title compound **2.44** as a colourless liquid (0.22 g, 100% conversion, 89% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.87-7.82 (3H, m, ArH), 7.70 (1H, s, ArH), 7.52-7.48 (m, 2H, ArH), 7.40 (1H, dd,  $J = 8.4, 1.6$  Hz, ArH), 7.27-7.20 (m, 2H, ArH), 6.76 (1H, t,  $J = 7.3$  Hz, ArH), 6.67 (2H, d,  $J = 8.6$  Hz, ArH), 3.53 (2H, t,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_2\text{NH}$ ), 3.11 (2H, t,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_2\text{NH}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  147.8 (C), 136.7 (C), 133.5 (C), 132.2 (C), 129.3 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.1 (CH), 125.5 (CH), 117.6 (CH), 113.1 (CH), 44.9 ( $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{18}\text{H}_{17}\text{N}$   $[\text{M}+\text{H}]^+$ : 248.1439. Found: 248.1446.



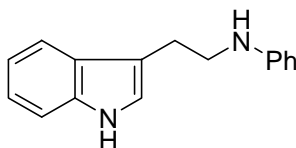
*N*-(2-(3,4-Dimethoxyphenyl)ethyl)aniline<sup>[13]</sup> **2.46** (Entry 4, Table 2.10)



Following **general procedure VIII with base**, 3,4-dimethoxyphenethyl alcohol (0.18 g, 1 mmol) was used in the reaction. The product was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (9:1),  $R_f$  = 0.12, to give the title compound **2.46** as an orange liquid (0.22 g, 100% conversion, 87% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.22 (2H, ddd,  $J$  = 8.0, 7.4, 1.2 Hz, ArH), 6.87-6.72 (4H, m, ArH), 6.64 (2H, dd,  $J$  = 7.6, 1.0 Hz, 1H, ArH), 3.90 (3H, s,  $\text{OCH}_3$ ), 3.89 (3H, s,  $\text{OCH}_3$ ), 3.41 (2H, t,  $J$  = 6.9 Hz,  $\text{CH}_2\text{CH}_2\text{NH}$ ), 2.89 (2H, t,  $J$  = 6.9 Hz,  $\text{CH}_2\text{CH}_2\text{NH}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  148.9 (C), 147.9 (C), 147.5 (C), 131.7 (C), 129.1 (CH), 120.6 (CH), 117.3 (CH), 112.9 (CH), 111.9 (CH), 111.3 (CH), 55.8 ( $\text{CH}_3$ ), 55.7 ( $\text{CH}_3$ ), 45.0 ( $\text{CH}_2$ ), 34.9 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{16}\text{H}_{20}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 258.1494. Found: 258.1490.

Following **general procedure VIII without base**, 3,4-dimethoxyphenethyl alcohol (0.18 g, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (100% conversion).

*N*-(2-(Indol-3-yl)ethyl)aniline **2.48** (Entry 5, Table 2.10)

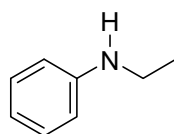


Following **general procedure VIII with base**, tryptophol (0.16 g, 1 mmol) was used in the reaction. The reaction mixture was filtered through Celite<sup>®</sup> and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Conversion was determined by analysis of the  $^1\text{H}$  NMR spectrum (100% conversion). The product was obtained and purified by column chromatography eluting with dichloromethane/hexane (9:1),  $R_f$  = 0.49, to give the title compound **2.48** as a colourless liquid (0.16 g, 100% conversion, 70% yield);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  8.01 (br. s, 1H, NH), 7.65 (1H, d,  $J$  = 7.8, ArH),

7.40 (1H, d,  $J = 8.1$ , ArH), 7.27-7.13 (4H, m, ArH), 7.13 (1H, s, ArH), 6.73 (1H, t,  $J = 7.3$  Hz, ArH), 6.65 (2H, d,  $J = 7.7$  Hz, ArH), 3.50 (2H, t,  $J = 6.8$  Hz, CH<sub>2</sub>CH<sub>2</sub>NH), 3.12 (2H, t,  $J = 6.8$  Hz, CH<sub>2</sub>CH<sub>2</sub>NH); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C): δ 148.0 (C), 136.3 (C), 129.2 (CH), 127.4 (C), 122.2 (CH), 122.0 (CH), 119.4 (CH), 118.8 (CH), 117.4 (C), 113.4 (C), 113.1 (CH), 111.2 (CH), 44.0 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>). ESI-MS: Calculated for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 237.1392. Found: 237.1381.

Following **general procedure VIII without base**, tryptophol (0.16 g, 1 mmol) was used in the reaction. The solvents were concentrated *in vacuo* to yield a brown crude mixture. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (100% conversion).

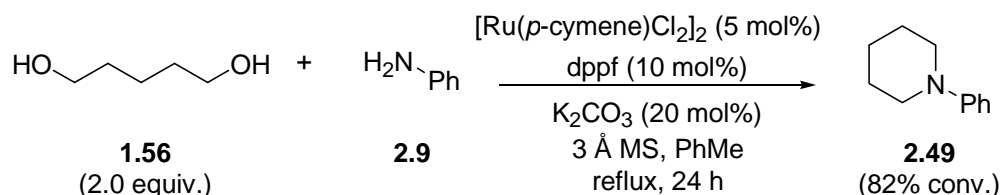
*N*-Ethylaniline<sup>[8]</sup> **2.35** (Scheme 2.18)



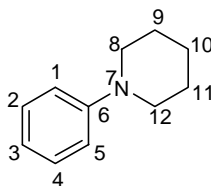
Procedure **with base** has already been described earlier (Section 5.2.8).

Following **general procedure VIII without base**, absolute ethanol (0.31 mL, 4.8 equiv., 5.28 mmol) was used in the reaction. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a reddish-brown crude mixture. Reaction conversion was determined by analysis of the peak integral ratios characteristic of *N*-ethylaniline **2.35** and *N,N*-diethylaniline **2.36** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

### 5.2.12 Procedure for the Cyclisation of Diols with Aniline



*N*-(Phenyl)piperidine<sup>[11]</sup> **2.49** (Entry 6, Table 2.10)



**With base:**

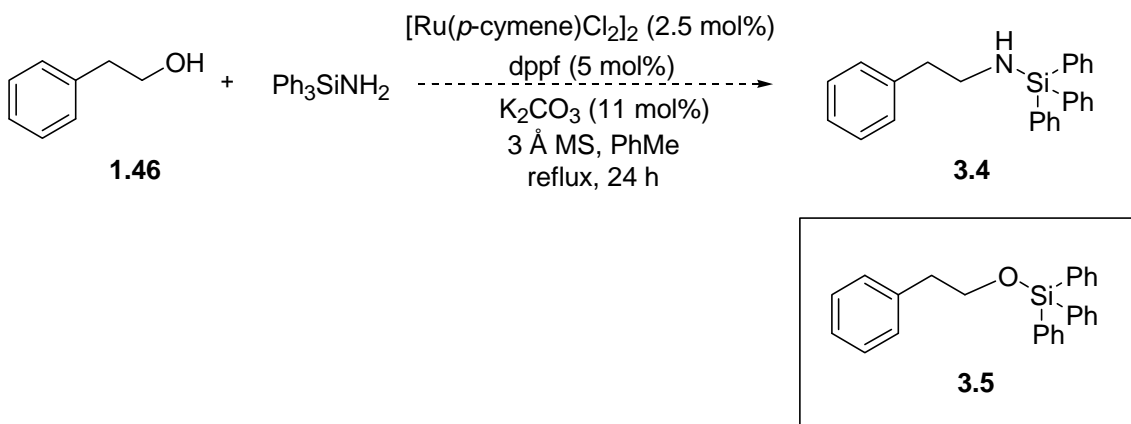
[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aniline (46 µL, 0.5 mmol), 1,5-pentanediol (105 µL, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was filtered through Celite® and washed with dichloromethane. The filtrate was collected and the solvents were concentrated *in vacuo* to yield a blood-red crude mixture. Purification by column chromatography eluting with hexane/ethyl acetate (20:1), *R<sub>f</sub>* = 0.10, gave the title compound **2.49** as a colourless liquid (81 mg, 65% yield); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C): δ 7.17 (2H, m, ArH), 6.87 (2H, dd, *J* = 8.7, 0.90 Hz, ArH), 6.74 (1H, tt, *J* = 7.3, 1.0 Hz, ArH), 3.08 (4H, t, *J* = 5.5 Hz, H<sub>8</sub>, H<sub>12</sub>), 1.67-1.60 (4H, m, H<sub>9</sub>, H<sub>11</sub>), 1.54-1.45 (2H, m, H<sub>10</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C): δ 152.66 (C), 129.41 (CH), 119.60 (CH), 116.95 (CH), 51.11 (CH<sub>2</sub>), 26.28 (CH<sub>2</sub>), 24.73 (CH<sub>2</sub>). ESI-MS: Calculated for C<sub>11</sub>H<sub>16</sub>N [M+H]<sup>+</sup>: 162.1283. Found: 162.1277.

**Without base and 3 Å MS:**

[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol) and dppf (27.7 mg, 0.05 mmol) were added to a Young's tap carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aniline (91 µL, 1 mmol), 1,5-pentanediol (130 µL, 1.2 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and the solvents were concentrated *in vacuo*. Conversion was determined by analysis of the <sup>1</sup>H NMR spectrum (84% conversion).

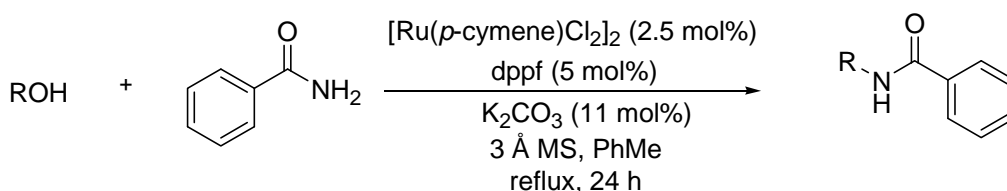
### 5.3 Experimental Procedures for Chapter 3

#### 5.3.1 Procedure for the Attempted Ruthenium-Catalysed *N*-Alkylation of Aminotriphenylsilane with Phenethyl Alcohol as Summarised in Scheme 3.5



[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (15.2 mg, 0.055 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a Radley's carousel tube and the mixture was exposed to nitrogen for 10 minutes. Aminotriphenylsilane (0.28 g, 1 mmol), phenethyl alcohol (119 µL, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to 110 °C for 24 hours. The resulting brown crude mixture was left to cool to room temperature, diluted with dichloromethane and the solvents were concentrated *in vacuo*. ESI-MS spectrum confirmed the presence of triphenylsilylated phenethyl alcohol: Calculated for C<sub>26</sub>H<sub>24</sub>OSi [M+H]<sup>+</sup>: 381.1669. Found: 381.1682.

#### 5.3.2 General Procedure I for the Attempted Ruthenium-Catalysed *N*-Alkylation of Benzamide with Primary Alcohols as Summarised in Table 3.1



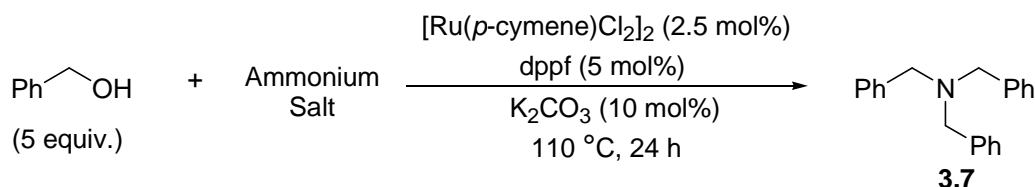
[Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (15.2 mg, 0.055 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a Radley's carousel tube and the mixture was exposed to nitrogen for 10 minutes. Benzamide (0.12 g, 1 mmol), phenethyl alcohol (119 µL, 1 mmol) and anhydrous toluene (1 mL) were added dropwise and the reaction mixture was allowed to stir under nitrogen at

room temperature for 10 minutes before being heated to 110 °C for 24 hours. The resulting brown crude mixture was left to cool to room temperature, diluted with dichloromethane and the solvents were concentrated *in vacuo*. Conversion was determined by analysis of the peak integral ratios characteristic of benzamide **3.6** and *N*-phenethylbenzamide in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### Variation of Primary Alcohols

Following **general procedure I**, phenethyl alcohol was exchanged for the different primary alcohols according to the number of equivalents used in the reaction as described in Table 3.1.

### 5.3.3 General Procedure II for the Ruthenium-Catalysed *N*-Alkylation of Ammonium Salts with Primary Alcohols by Borrowing Hydrogen as Summarised in Table 3.2



To an oven-dried, nitrogen purged Radley's carousel tube containing [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppe (27.7 mg, 0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (13.8 mg, 0.10 mmol), ammonium acetate (77.1 mg, 1 mmol) and activated molecular sieves (0.52 g, 3 Å) was added benzyl alcohol (0.52 mL, 5 mmol) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The resulting crude was evaporated *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of benzyl alcohol **1.52** and tribenzylamine **3.7** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

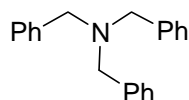
### Variation of Ammonium Salts

Following **general procedure II**, ammonium acetate was exchanged for the different ammonium salts described in Table 3.1.

### Variation of Primary Alcohols

Following **general procedure II**, benzyl alcohol was exchanged for the different primary alcohols described in Figure 3.1.

Tribenzylamine<sup>[14]</sup> **3.7** (Entry 1, Table 3.2)



Following **general procedure II**, the resulting crude was evaporated *in vacuo* and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/diethyl ether (98:2),  $R_f = 0.17$ , to give the title compound **3.7** as a white solid (0.19 g, 68%), m.p. 93-94 °C;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.43-7.21 (15H, m, ArH), 3.57 (6H, s,  $\text{N}(\text{CH}_2\text{Ph})_3$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  140.1 (C), 129.2 (CH), 128.6 (CH), 127.3 (CH), 58.3 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{21}\text{H}_{22}\text{N}$   $[\text{M}+\text{H}]^+$ : 288.1752. Found: 288.1750.

### 5.3.4 General Procedure III for the Ruthenium-Catalysed *N*-Alkylation of Amine Acetate with Benzyl Alcohol by Borrowing Hydrogen as Summarised in Scheme 3.9

#### Representative Preparation of Amine acetate:

To a solution of glacial acetic acid (0.27 mL, 4.6 mmol) in diethyl ether (10 mL) was added benzyl amine (0.5 mL, 4.6 mmol) dropwise in a 25 mL RBF. A white precipitate was formed immediately and filtered to give benzyl ammonium acetate (0.54 g, 71%).

#### Representative procedure for the amination of benzyl alcohol with amine acetate:

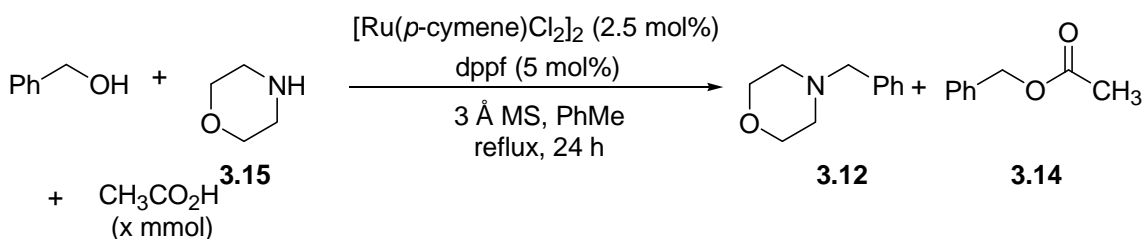
To an oven-dried, nitrogen purged Radley's carousel tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppe (27.7 mg, 0.05 mmol), benzyl ammonium acetate (77.1 mg, 1 mmol) and activated molecular sieves (0.52 g, 3 Å) was added benzyl alcohol (0.52 mL, 5 mmol) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The resulting crude was evaporated *in vacuo* and side products were identified by the analysis of the  $^1\text{H}$  NMR spectrum.

#### Screening with Base, No Base and No Solvent

Following **general procedure III**, morpholinium acetate was prepared. Benzyl ammonium acetate was exchanged for the morpholinium acetate as described in Table

3.3. Screening was carried out according to the conditions described in Table 3.3. The resulting crude was evaporated *in vacuo* and side products were identified by the analysis of the peak integral ratios characteristic of *N*-benzylmorpholine **3.12**, benzaldehyde **3.13** and benzyl acetate **3.14** in the  $^1\text{H}$  NMR spectrum.

### 5.3.5 General Procedure IV for the Ruthenium-Catalysed *N*-Alkylation of Morpholine in the Presence of Glacial Acetic Acid with Benzyl Alcohol by Borrowing Hydrogen as Summarised in Table 3.4

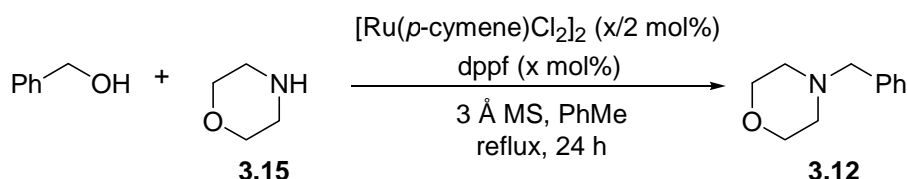


To an oven-dried, nitrogen purged Radley's carousel tube containing  $[\text{Ru(p-cymene)Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) was added morpholine (87  $\mu\text{L}$ , 1 mmol), glacial acetic acid (57  $\mu\text{L}$ , 1 mmol) and benzyl alcohol (0.52 mL, 5 mmol) dropwise. Anhydrous toluene (1 mL) was added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to 110  $^\circ\text{C}$  for 24 hours. The resulting crude was evaporated *in vacuo* and side products were identified by the analysis of the peak integral ratios characteristic of *N*-benzylmorpholine **3.12** and benzyl acetate **3.13** in the  $^1\text{H}$  NMR spectrum.

#### Variation of Glacial Acetic Acid

Following **general procedure IV**, different amounts of glacial acetic acid was added as described in Table 3.4.

### 5.3.6 General Procedure V for the Ruthenium-Catalysed *N*-Alkylation of Morpholine with Benzyl Alcohol by Borrowing Hydrogen as Summarised in Table 3.5

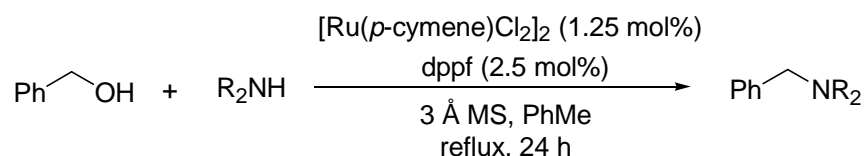


To an oven-dried, nitrogen purged Radley's carousel tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) was added morpholine (87 µL, 1 mmol) and benzyl alcohol (0.52 mL, 5 mmol) dropwise. Anhydrous toluene (1 mL) was added dropwise and the reaction mixture was allowed to stir under nitrogen at room temperature for 10 minutes before being heated to reflux for 24 hours. The resulting crude was evaporated *in vacuo* and side products were identified by the analysis of the  $^1\text{H}$  NMR spectrum.

### Variation of Catalyst Loading

Following **general procedure V**, catalyst loading were varied at 4 mol% of Ru {12.2 mg, 0.020 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ }, 2.5 mol% of Ru {7.7 mg, 0.0125 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } and 1 mol% of Ru {3.1 mg, 0.005 mmol,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ } as described in Table 3.5. Reaction conversion was determined by the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

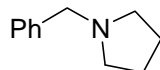
### 5.3.7 General Procedure VI for the Ruthenium-Catalysed *N*-Alkylation of Secondary Amines with Benzyl Alcohol by Borrowing Hydrogen as Summarised in Table 3.6



To an oven-dried, nitrogen purged Radley's carousel tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (7.7 mg, 0.0125 mmol), dppf (13.9 mg, 0.025 mmol) and activated molecular sieves (0.52 g, 3 Å) was added the representative amine (1 mmol), benzyl alcohol (103 µL, 1 mmol) followed by anhydrous toluene (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The resulting crude was evaporated *in vacuo*. The crude product was purified by column chromatography to give the corresponding tertiary amine in good yields.

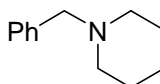


*N*-Benzylpyrrolidine<sup>[5]</sup> **3.17** (Entry 1, Table 1)



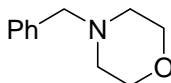
Following **general procedure VI**, using pyrrolidine (83  $\mu$ L, 1 mmol), the title compound **3.17** was obtained and purified by column chromatography eluting with diethyl ether,  $R_f = 0.05$  to give a reddish-brown oil (0.11 g, 71%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.37-7.23 (5H, m, ArH), 3.63 (2H, s, PhCH<sub>2</sub>), 2.55-2.49 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>), 1.83-1.75 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  139.4 (C), 128.9 (CH), 128.2 (CH), 126.8 (CH), 60.8 (CH<sub>2</sub>), 54.2 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>); ESI-MS: Calculated for  $\text{C}_{11}\text{H}_{16}\text{N}$   $[\text{M}+\text{H}]^+$ : 162.1283. Found: 162.1287.

*N*-Benzylpiperidine<sup>[5]</sup> **3.19** (Entry 2, Table 1)



Following **general procedure VI**, using piperidine (99  $\mu$ L, 1 mmol), the title compound **3.19** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^\circ\text{C}$ )/ethyl acetate (5:1),  $R_f = 0.09$  to give a light orange oil (0.13 g, 72%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.40-7.21 (5H, m, ArH), 3.49 (2H, s, PhCH<sub>2</sub>), 2.39-2.37 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.63-1.55 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.48-1.43 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  129.3 (CH), 128.1 (CH), 126.9 (CH), 63.8 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>).<sup>[15]</sup> ESI-MS: Calculated for  $\text{C}_{12}\text{H}_{18}\text{N}$   $[\text{M}+\text{H}]^+$ : 176.1439. Found: 176.1435.

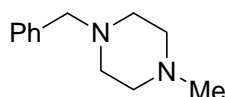
*N*-Benzylmorpholine<sup>[16]</sup> **3.12** (Entry 3, Table 3.6)



Following **general procedure VI**, using morpholine (87  $\mu$ L, 1 mmol), the title compound **3.12** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^\circ\text{C}$ )/ethyl acetate (4:1),  $R_f = 0.16$  to give a clear colourless oil (0.15 g, 84%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.29-7.21 (5H, m, ArH), 3.67

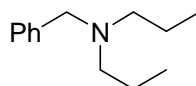
(4H, t,  $J = 4.8$  Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.46 (2H, s,  $\text{PhCH}_2$ ), 2.40 (4H, t,  $J = 4.6$  Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  137.7 (C), 129.2 (CH), 128.2 (CH), 127.1 (CH), 67.0 ( $\text{CH}_2$ ), 63.5 ( $\text{CH}_2$ ), 53.6 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{11}\text{H}_{16}\text{NO} [\text{M}+\text{H}]^+$ : 178.1232. Found: 178.1223.

1-Benzyl-4-methylpiperazine **3.21** (Entry 4, Table 3.6)



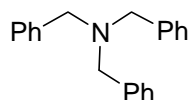
Following **general procedure VI**, using *N*-methylpiperazine (111  $\mu\text{L}$ , 1 mmol), the title compound **3.21** was obtained and purified by column chromatography eluting with petroleum ether dichloromethane/methanol (9:1),  $R_f = 0.16$  to give a pale yellow liquid (0.15 g, 80%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.32-7.24 (5H, m, ArH), 3.51 (2H, s,  $\text{PhCH}_2$ ), 2.48 (8H, br. s,  $\text{NCH}_2\text{CH}_2\text{N}$ ), 2.92 (3H, s,  $\text{CH}_3$ );<sup>[17]</sup>  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  138.1 (C), 129.2 (CH), 128.2 (CH), 127.0 (CH), 63.0 ( $\text{CH}_2$ ), 55.1 ( $\text{CH}_2$ ), 52.9 ( $\text{CH}_2$ ), 45.9 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{12}\text{H}_{19}\text{N}_2 [\text{M}+\text{H}]^+$ : 191.1548. Found: 191.1544.

*N,N*-Dipropylbenzylamine<sup>[18]</sup> **3.23** (Entry 5, Table 3.6)



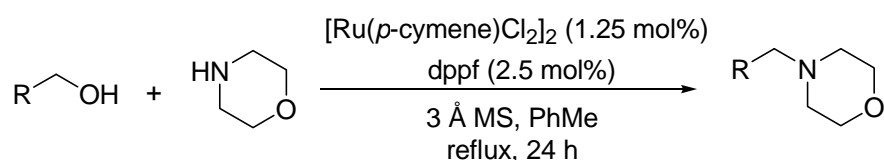
Following **general procedure VI**, using dipropylamine (137  $\mu\text{L}$ , 1 mmol), the title compound **3.23** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (9:1),  $R_f = 0.24$  to give a colourless oil (0.17 g, 87%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.37-7.23 (5H, m, ArH), 3.57 (2H, s,  $\text{PhCH}_2$ ), 2.34 (4H, t,  $J = 7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 1.57-1.42 (4H, sextet,  $J = 7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 0.87 (6H, t,  $J = 7.3$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  128.8 (CH), 126.6 (C), 128.0 (CH), 58.6 ( $\text{CH}_2$ ), 55.8 ( $\text{CH}_2$ ), 20.2 ( $\text{CH}_2$ ), 11.9 ( $\text{CH}_3$ ).<sup>[15]</sup> ESI-MS: Calculated for  $\text{C}_{13}\text{H}_{22}\text{N}$   $[\text{M}+\text{H}]^+$ : 192.1752. Found: 192.1740.

Tribenzylamine<sup>[14]</sup> **3.7** (Entry 6, Table 3.6)



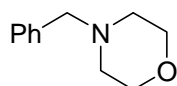
Following **general procedure VI**, using dibenzylamine (192  $\mu$ L, 1 mmol), the title compound **3.7** was obtained and purified by column chromatography petroleum ether (b.p. 40-60  $^{\circ}$ C)/diethyl ether (98:2),  $R_f$  = 0.17, to give a white solid (0.13 g, 44%). The spectroscopy data was consistent with the analytical data reported previously (Entry 1, Table 3.2).

### 5.3.8 General Procedure VII for the Ruthenium-Catalysed *N*-Alkylation of Morpholine with Primary Alcohols by Borrowing Hydrogen as Summarised in Table 3.7



To an oven-dried, nitrogen purged carousel tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (7.7 mg, 0.0125 mmol), dppe (13.9 mg, 0.025 mmol) and activated molecular sieves (0.52 g, 3  $\text{\AA}$ ) was added morpholine (87  $\mu$ L, 1 mmol), the representative alcohol (1 mmol) followed by anhydrous toluene (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The resulting crude was evaporated *in vacuo*. The crude product was purified by column chromatography to yield the corresponding alkylated morpholine products in good yields.

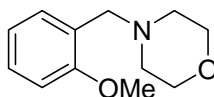
*N*-Benzylmorpholine<sup>[16]</sup> **3.12** (Entry 1, Table 3.7)



Following **general procedure VII**, using benzyl alcohol (103  $\mu$ L, 1 mmol), the title compound **3.12** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^{\circ}$ C)/ethyl acetate (4:1),  $R_f$  = 0.16 to give a clear colourless

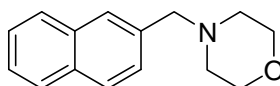
oil (0.15 g, 84%). The spectroscopy data was consistent with the analytical data reported previously (Entry 3, Table 3.6).

4-(2-Methoxybenzyl)morpholine **3.24** (Entry 2, Table 3.7)



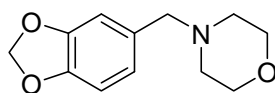
Following **general procedure VII**, using 2-methoxybenzyl alcohol (133  $\mu$ L, 1 mmol), the title compound **3.24** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^{\circ}$ C)/ethyl acetate (5:1),  $R_f$  = 0.07 to give a clear pale yellow oil (0.15 g, 74%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  7.37 (1H, d,  $J$  = 7.4, ArH), 7.28-7.22 (1H, m ArH), 6.94 (1H, app. t,  $J$  = 7.4 Hz, ArH), 6.89 (1H, d,  $J$  = 8.2 Hz, ArH), 3.84 (3H, s,  $\text{OCH}_3$ ), 3.74 (4H, t,  $J$  = 4.7 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.58 (2H, s,  $\text{PhCH}_2$ ), 2.52 (4H, t,  $J$  = 4.6 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  157.9 (C), 130.6 (CH), 128.2 (CH), 125.7 (C), 120.3 (CH), 110.5 (CH), 67.0 ( $\text{CH}_2$ ), 56.4 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 53.6 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{12}\text{H}_{18}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 208.1338. Found: 208.1332.

*N*-(Naphthylmethyl)morpholine<sup>[19]</sup> **3.25** (Entry 3, Table 3.7)



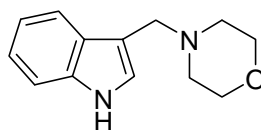
Following **general procedure VII**, using 2-naphthalenemethanol (0.16 g, 1 mmol), the title compound **3.25** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^{\circ}$ C)/ethyl acetate (2:1),  $R_f$  = 0.28 to give a clear yellowish-brown liquid (0.18 g, 78%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  7.85-7.81 (3H, ArH), 7.76 (1H, s, ArH), 7.54-7.46 (3H, ArH), 3.74 (4H, t,  $J$  = 4.5 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.68 (2H, s,  $\text{PhCH}_2$ ), 2.51 (4H, t,  $J$  = 4.5 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  135.3 (C), 133.3 (C), 132.8 (C), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 126.0 (CH), 125.7 (CH), 67.0 ( $\text{CH}_2$ ), 63.6 ( $\text{CH}_2$ ), 53.7 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{15}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 228.1388. Found: 228.1380.

Piperonylmorpholine<sup>[20]</sup> **3.27** (Entry 4, Table 3.7)



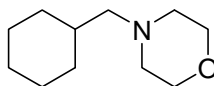
Following **general procedure VII**, using piperonyl alcohol (0.15 g, 1 mmol), the title compound **3.27** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (2:1),  $R_f = 0.29$  to give a clear pale yellow liquid (0.20 g, 89%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  6.87 (1H, s, ArH), 6.75 (2H, br. s, ArH), 5.95 (2H, s,  $\text{OCH}_2\text{O}$ ), 3.71 (4H, t,  $J = 4.6$  Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.41 (2H, s,  $\text{PhCH}_2$ ), 2.43 (4H, t,  $J = 4.5$  Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  147.6 (C), 146.6 (C), 131.7 (C), 122.2 (CH), 109.5 (CH), 107.8 (CH), 100.9 ( $\text{CH}_2$ ), 67.1 ( $\text{CH}_2$ ), 63.2 ( $\text{CH}_2$ ), 53.4 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{12}\text{H}_{16}\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 222.1130. Found: 222.1144.

3-Morpholin-4-ylmethyl-indole<sup>[21]</sup> **3.28** (Entry 5, Table 3.7)



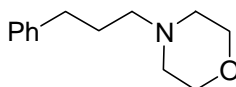
Following **general procedure VII**, using indole-3-carbinol (0.15 g, 1 mmol) the title compound **3.28** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (1:2),  $R_f = 0.12$  to give a pale brown solid (0.18 g, 85%); m.p. 119-120 °C (Lit.<sup>[21]</sup> m.p. 121-123 °C);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  8.15 (1H, br. s, NH), 7.78 (1H, d,  $J = 7.8$  Hz, ArH), 7.38 (1H, d,  $J = 8.4$  Hz, ArH), 7.25-7.12 (3H, ArH), 3.73 (2H, s,  $\text{PhCH}_2$ ), 3.74-3.71 (4H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.52 (4H, t,  $J = 4.6$  Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  136.3 (C), 127.9 (C), 123.6 (CH), 122.1 (CH), 119.6 (CH), 119.5 (CH), 112.3 (C), 111.0 (CH), 67.1 ( $\text{CH}_2$ ), 54.0 ( $\text{CH}_2$ ), 53.6 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 217.1341. Found: 217.1330.

*N*-(Cyclohexylmethyl)morpholine<sup>[22]</sup> **3.30** (Entry 6, Table 3.7)



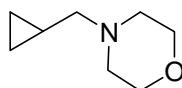
Following **general procedure VII**, using cyclohexylmethanol (123  $\mu$ L, 1 mmol), the title compound **3.30** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (3:4),  $R_f$  = 0.49 to give a clear pale brown oil (0.11 g, 62%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  3.71 (4H, t,  $J$  = 4.7 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.38 (4H, t,  $J$  = 4.5 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.12 (2H, d,  $J$  = 7.2 Hz,  $\text{CHCH}_2\text{N}$ ), 1.80-1.69 (4H, m,  $\text{CH}_2$ ), 1.56-1.42 (1H, m,  $\text{CHCH}_2\text{N}$ ), 1.29-1.14 (4H, m,  $\text{CH}_2$ ), 0.94-0.82 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  67.1 ( $\text{CH}_2$ ), 66.2 ( $\text{CH}_2$ ), 54.2 ( $\text{CH}_2$ ), 34.7 (CH), 31.8 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{11}\text{H}_{22}\text{NO}$   $[\text{M}+\text{H}]^+$ : 184.1701. Found: 184.1695.

4-(3-Phenyl-propyl)-morpholine<sup>[23]</sup> **3.32** (entry 7, Table 3.7)



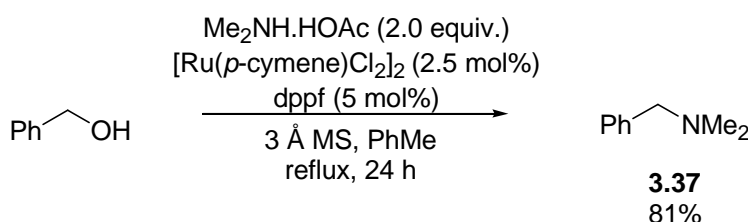
Following **general procedure VII**, using 3-phenylpropyl alcohol (135  $\mu$ L, 1 mmol), the title compound **3.32** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/ethyl acetate (1:1),  $R_f$  = 0.24 to give a pale brown liquid (0.16 g, 77%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.27-7.11 (5H, m, ArH), 3.68 (4H, t,  $J$  = 4.7 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.61 (2H, t,  $J$  = 7.7 Hz,  $\text{PhCH}_2$ ), 2.41-2.38 (4H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.33 (2H, t,  $J$  = 7.6 Hz,  $\text{CH}_2$ ), 1.84-1.72 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  142.0 (C), 128.4 (CH), 128.3 (CH), 125.8 (CH), 67.0 ( $\text{CH}_2$ ), 58.4 ( $\text{CH}_2$ ), 53.7 ( $\text{CH}_2$ ), 33.6 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{13}\text{H}_{20}\text{NO}$   $[\text{M}+\text{H}]^+$ : 206.1545. Found: 206.1545.

4-(3-Phenyl-propyl)morpholine<sup>[24]</sup> **3.34** (entry 8, Table 3.7)



Following **general procedure VII**, using cyclopropanemethanol (81  $\mu$ L, 1 mmol), the title compound **3.34** was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60  $^{\circ}$ C)/ethyl acetate (1:2),  $R_f$  = 0.06 to give a clear pale yellowish-brown oil (0.12 g, 85%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  3.75 (4H, t,  $J$  = 6.5 Hz,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.55-2.51 (4H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.25 (2H, d,  $J$  = 6.5 Hz,  $\text{CHCH}_2\text{N}$ ), 0.94-0.79 (1H, m,  $\text{CH}$ ), 0.56-0.49 (2H, m,  $\text{CH}_2$ ), 0.14-1.10 (2H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^{\circ}$ C):  $\delta$  66.9 ( $\text{CH}_2$ ), 64.1 ( $\text{CH}_2$ ), 53.8 ( $\text{CH}_2$ ), 30.9 ( $\text{CH}$ ), 8.1 ( $\text{CH}_2$ ), 3.8 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_8\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 142.1232. Found: 142.1250.

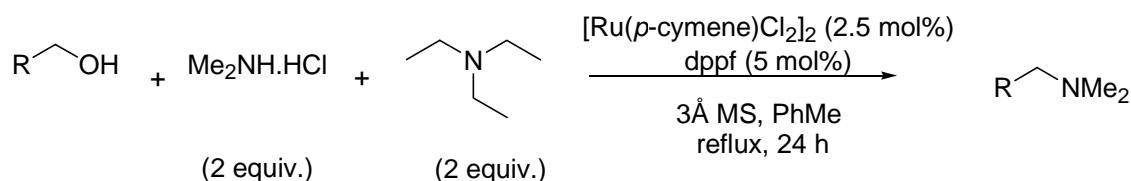
### 5.3.9 Preparation of *N,N*-Dimethylbenzylamine **3.37** (Scheme 3.11)



Dimethylammonium acetate was prepared according to general procedure III. To an oven-dried, nitrogen purged Schlenk tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol),  $\text{K}_2\text{CO}_3$  (13.8 mg, 0.10 mmol) and activated molecular sieves (0.52 g, 3  $\text{\AA}$ ) was added benzyl alcohol (0.21 mL, 2 mmol), dimethylammonium acetate (0.11 mL, 1 mmol) and anhydrous toluene dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and HCl (1.5 M, 20 mL) was added to the crude mixture and then extracted two times with  $\text{CH}_2\text{Cl}_2$  (50 mL) to remove any excess benzyl alcohol. In order to isolate the amine, the combined aqueous HCl layers were neutralised with NaOH (1.5 M, 25 mL, pH = 8) and then extracted two times with  $\text{CH}_2\text{Cl}_2$  (50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous  $\text{MgSO}_4$  and the solvent was removed *in vacuo* to form a clear light yellow oil (0.11 g, 82%);  $^1\text{H}$  NMR

(250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.31 (5H, m, ArH), 3.43 (2H, s,  $\text{PhCH}_2$ ), 2.24 (6H, s,  $\text{N}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  138.8 (C), 129.1 (CH), 128.2 (CH), 127.0 (CH), 64.4 ( $\text{CH}_2$ ), 45.4 ( $\text{CH}_3$ ). This is consistent with literature data.<sup>[25]</sup> ESI-MS: Calculated for  $\text{C}_9\text{H}_{14}\text{N}$   $[\text{M}+\text{H}]^+$ : 136.1126. Found: 136.1130.

### 5.3.10 General Procedure VIII for the Dimethylation of Primary Alcohols with Dimethylamine Acetate by Borrowing Hydrogen (Table 3.8)

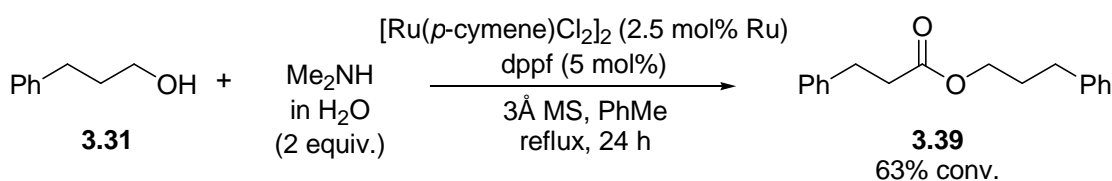


To an oven-dried, nitrogen purged Schlenk tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), dimethylammonium chloride (0.16 g, 2 mmol) and activated molecular sieves (0.52 g, 3 Å) was added benzyl alcohol (103  $\mu\text{L}$ , 1 mmol) and triethylamine (279  $\mu\text{L}$ , 2 mmol) followed by anhydrous toluene (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of benzyl alcohol and *N,N*-dimethylbenzylamine **3.37** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

#### Variation of Primary Alcohols

Following **general procedure VIII**, benzyl alcohol was exchanged for the different alcohols described in Table 3.8.

### 5.3.11 Dimethylation of 3-Phenylpropyl Alcohol using Dimethylamine solution (40 wt. % in $\text{H}_2\text{O}$ ) by Borrowing Hydrogen (Scheme 3.13)

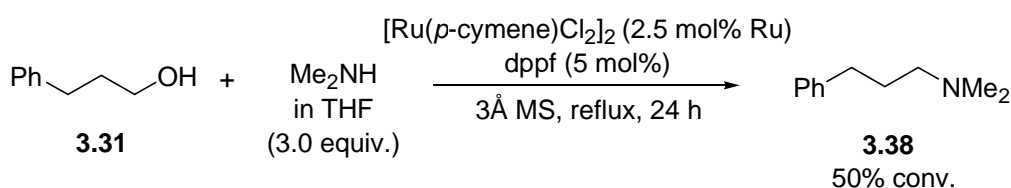


To an oven-dried, nitrogen purged Ace Pressure tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol) and activated molecular sieves



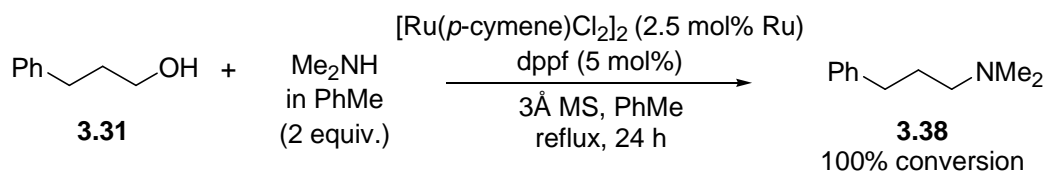
(0.52 g, 3 Å) was added anhydrous toluene (1 mL) dropwise and the mixture was set to reflux for 45 minutes (pre-mix catalyst used in order to avoid the deactivation of catalyst by water). Dimethylamine solution (40 wt. % in H<sub>2</sub>O) (250 µL, 2 mmol) and 3-phenyl propyl alcohol (135 µL, 1 mmol) were added dropwise. The reaction mixture was heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of the ester **3.39** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

### 5.3.12 Dimethylation of 3-Phenylpropyl Alcohol using Dimethylamine solution (2.0 M solution in THF) by Borrowing Hydrogen (Scheme 3.14)



To an oven-dried, nitrogen purged Ace Pressure tube containing [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol) and activated molecular sieves (0.52 g, 3 Å) was added 3-phenylpropyl alcohol (135 µL, 1 mmol) followed by dimethylamine solution (2.0 M solution in THF) (150 µL, 3 mmol) dropwise. The reaction mixture was heated to 100 °C for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of the amine product **3.38** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

### 5.3.13 Dimethylation of 3-Phenylpropyl Alcohol using Dimethylamine in Toluene by Borrowing Hydrogen (Scheme 3.15)



#### Preparation of Dimethylamine Solution in Toluene by Extraction:

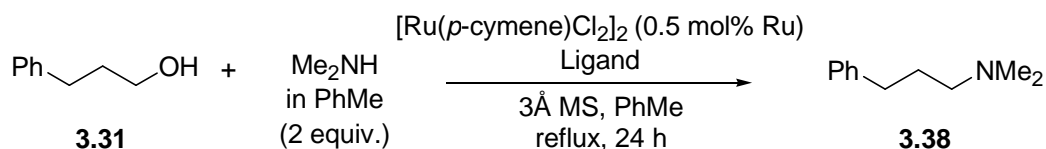
Dimethylamine solution (40 wt. % in H<sub>2</sub>O) (2.50 mL) and anhydrous toluene (6 mL) were added to a 25 mL separating flask. After the flask was shaken twice, the

dimethylamine-toluene layer was pipetted out and dried with anhydrous  $\text{MgSO}_4$ . Concentration was found to be 0.56 mmol of  $\text{Me}_2\text{NH}$ /1 mL of toluene (confirmed by comparison of the methyl groups signal by  $^1\text{H}$  NMR spectroscopy).

### Dimethylation by Borrowing Hydrogen:

To an oven-dried, nitrogen purged Schlenk tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (3.8 mg, 0.00625 mmol), dppf (6.9 mg, 0.0125 mmol) and activated molecular sieves (0.52 g, 3 Å) was added 3-phenylpropyl alcohol (34  $\mu\text{L}$ , 0.25 mmol) followed by dimethylamine solution (0.56 M solution in Toluene) (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of *N,N*-dimethyl-3-phenylpropyl amine **3.38** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

#### 5.3.14 General Procedure IX for the Dimethylation of 3-Phenylpropyl Alcohol using Dimethylamine in Toluene by Varying Ligand Loading by Borrowing Hydrogen as Summarised in Table 3.9



Dimethylamine in toluene was prepared according to procedure 6.3.13. To an oven-dried, nitrogen purged Schlenk tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (0.8 mg, 0.00125 mmol), dppf (1.4 mg, 0.0025 mmol) and activated molecular sieves (0.52 g, 3 Å) was added 3-phenylpropyl alcohol (34  $\mu\text{L}$ , 0.25 mmol) followed by dimethylamine solution (0.56 M solution in Toluene) (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of 3-phenylpropyl alcohol and *N,N*-dimethyl-3-phenylpropyl amine **3.38** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### Variation of dppf Loading

Following **general procedure IX**, dppf loading was varied at 0.5 mol% (0.7 mg, 0.00125 mmol) and 2 mol% (2.8 mg, 0.005 mmol) as described in Table 3.9, Section 3.5.

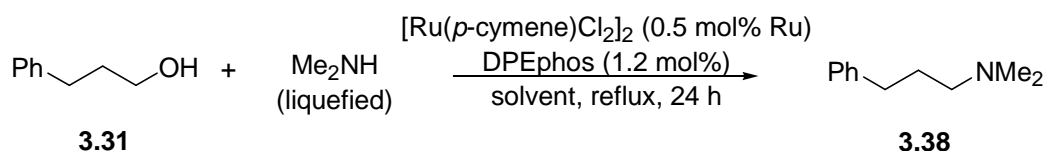
### Variation of Ligand Loading

Following **general procedure IX**, dppf was exchanged with DPEphos and PPh<sub>3</sub>. DPEphos loading was varied at 0.5 mol% (0.7 mg, 0.00125 mmol), 1 mol% (1.3 mg, 0.0025 mmol) and 2 mol% (2.7 mg, 0.005 mmol) as described in Table 3.9, Section 3.4. PPh<sub>3</sub> loading was varied at 1 mol% (0.7 mg, 0.0025 mmol), 2 mol% (1.3 mg, 0.005 mmol) and 4 mol% (2.6 mg, 0.01 mmol) as described in Table 3.9, Section 3.5.

### Variation of DPEphos Loading

Following **general procedure IX**, DPEphos loading was varied at 1.2 mol% (1.6 mg, 0.003 mmol) and 2 mol% (2.7 mg, 0.005 mmol) with and without activated molecular sieves (0.52 g, 3 Å) as described in Table 3.10, Section 3.5.

#### 5.3.15 General Procedure X for the Dimethylation of 3-Phenylpropyl Alcohol Using Liquefied Dimethylamine in Different Solvents by Borrowing Hydrogen as Summarised in Table 3.11

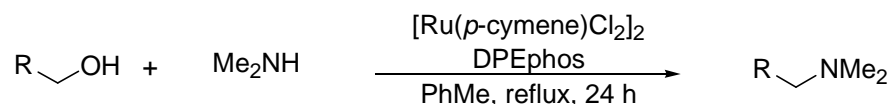


To an oven-dried, nitrogen purged Schlenk tube containing [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (1.9 mg, 0.00303 mmol), DPEphos (3.9 mg, 0.00731 mmol) was added 3-phenylpropyl alcohol (82 μL, 0.6 mmol), toluene (0.6 mL) followed by liquefied dimethylamine according to the total volume described in Table 3.11, Section 3.4. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of 3-phenylpropyl alcohol and *N,N*-dimethyl-3-phenylpropyl amine **3.38** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

### Variation of Solvent

Following **general procedure X**, toluene was exchanged with the different solvents described in Table 3.11, Section 3.4.

### 5.3.16 General Procedure XI for the Ruthenium-Catalysed Synthesis of *N,N*-Dimethylamines from Primary Alcohols Using Dimethylamine in Toluene as Summarised in Table 3.12



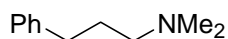
#### Preparation of Dimethylamine Solution in Toluene:

To an oven-dried, nitrogen-purged Schlenk tube containing liquefied dimethylamine gas (1.64 mL, condensed at -78 °C) was added anhydrous toluene (20 mL). The dimethylamine-toluene mixture was sealed and shaken and stored cold. Concentration was found to be 1.4 mmol of Me<sub>2</sub>NH/1 mL of toluene (confirmed by comparison of the methyl groups signal by <sup>1</sup>H NMR spectroscopy).

#### General Procedure for the Dimethylation of Primary Alcohols:

To an oven-dried, nitrogen-purged Schlenk tube containing [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (3.1 mg, 0.005 mmol) and DPEphos (6.6 mg, 0.012 mmol) was added alcohol (1 mmol) followed by a 1.4 M Me<sub>2</sub>NH solution in toluene (1 mL) dropwise. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol, furnishing the corresponding dimethylamino compounds.

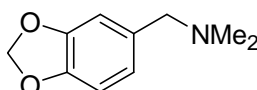
*N,N*-Dimethyl-3-phenylpropylamine<sup>[26]</sup> **3.38** (entry 1, Table 3.7)



Following **general procedure XI**, using 3-phenylpropyl alcohol (135 μL, 1 mmol), the title compound **3.38** was obtained and purified by column chromatography eluting with dichloromethane/methanol (92:8), *R<sub>f</sub>* = 0.15 to give a colourless oil (0.14 g, 83%); <sup>1</sup>H

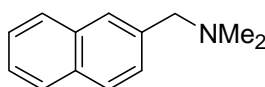
NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  7.37-7.32 (2H, m, ArH), 7.26-7.24 (3H, m, ArH), 2.70 (2H, t,  $J$  = 7.8 Hz, PhCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.37 (2H, t,  $J$  = 7.5 Hz, PhCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.23 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 1.86 (2H, tt,  $J$  = 7.8, 7.4 Hz, PhCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  142.3 (C), 128.4 (CH), 128.3 (CH), 125.7 (CH), 59.3 (CH<sub>2</sub>), 45.5 (CH<sub>3</sub>), 33.7 (CH<sub>2</sub>), 29.4(CH<sub>2</sub>). ESI-MS: Calculated for C<sub>11</sub>H<sub>18</sub>N [M+H]<sup>+</sup>: 164.1434. Found: 164.1425.

*N,N*-Dimethyl-3,4-(methylenedioxy)benzylamine<sup>[27]</sup> **3.40** (entry 2, Table 3.12)



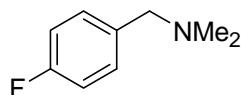
Following **general procedure XI**, using piperonyl alcohol (0.15 g, 1 mmol), the title compound **3.40** was obtained and purified by column chromatography eluting with dichloromethane/methanol (92:8),  $R_f$  = 0.15 to give an oil (0.15 g, 85%); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  6.84 (1H, s, ArH), 6.75 (2H, br. s, ArH), 5.95 (2H, s, OCH<sub>2</sub>O), 3.34 (2H, s, CH<sub>2</sub>), 2.23 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  147.6 (C), 146.6 (C), 132.7 (C), 122.2 (CH), 109.5 (CH), 107.9 (CH), 100.9 (CH<sub>2</sub>), 64.1 (CH<sub>2</sub>), 45.2 (CH<sub>3</sub>). ESI-MS: Calculated for C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 180.1025. Found: 180.1024.

*N,N*-Dimethyl-2-naphthalenemethanamine<sup>[28]</sup> **3.41** (entry 3, Table 3.7)



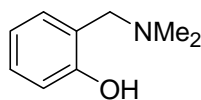
Following **general procedure XI**, using 2-naphthalenemethanol (0.16 g, 1 mmol), the title compound **3.41** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f$  = 0.34 to give a colourless oil (0.18 g, 97%); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  7.86-7.81 (3H, m, ArH), 7.75 (1H, s, ArH), 7.51-7.45 (3H, m, ArH), 3.60 (2H, s, CH<sub>2</sub>), 2.31 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  136.4 (C), 133.3 (C), 132.8 (C), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 125.9 (CH), 125.6 (CH), 64.5 (CH<sub>2</sub>), 45.5 (CH<sub>3</sub>). ESI-MS: Calculated for C<sub>13</sub>H<sub>16</sub>N [M+H]<sup>+</sup>: 186.1283. Found: 186.1271.

*N,N*-Dimethyl-4-fluorobenzylamine<sup>[28]</sup> **3.43** (entry 4, Table 3.7)



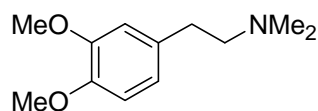
Following **general procedure XI**, using 4-fluorobenzyl alcohol (108  $\mu$ L, 1 mmol), the title compound **3.43** was obtained and purified by column chromatography eluting with dichloromethane/methanol (92:8),  $R_f$  = 0.16 to give a light yellow oil (90 mg, 60%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.30-7.24 (2H, m, ArH), 7.04-6.97 (2H, m, ArH), 3.39 (2H, s,  $\text{CH}_2$ ), 2.24 (6H, s,  $\text{N}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  162.0 (d,  $J_{\text{C-F}}$  = 244.9 Hz, C), 134.4 (d,  $J_{\text{C-F}}$  = 3.2 Hz, C), 130.6 (d,  $J_{\text{C-F}}$  = 8.0 Hz, CH), 115.0 (d,  $J_{\text{C-F}}$  = 21.2 Hz, CH), 63.5 ( $\text{CH}_2$ ), 45.2 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_9\text{H}_{13}\text{FN}$   $[\text{M}+\text{H}]^+$ : 154.1032. Found: 154.1023.

2-[(Dimethylamino)methyl]phenol<sup>[29]</sup> **3.45** (entry 5, Table 3.7)



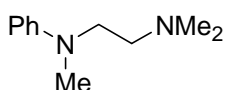
Following **general procedure XI**, using 2-hydroxybenzyl alcohol (0.12 g, 1 mmol), the title compound **3.45** was obtained and purified by column chromatography eluting with dichloromethane/methanol (95:5),  $R_f$  = 0.17 to give a light yellow oil (0.13 g, 88%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.21-7.15 (1H, m, ArH), 6.99-6.96 (1H, m, ArH), 6.86-6.75 (1H, m, ArH), 3.66 (2H, s,  $\text{CH}_2$ ), 2.35 (6H, s,  $\text{N}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  158.1 (C), 128.8 (CH), 128.4 (CH), 121.8 (C), 119.0 (CH), 116.1 (CH), 62.7 ( $\text{CH}_2$ ), 44.4 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_9\text{H}_{14}\text{NO}$   $[\text{M}+\text{H}]^+$ : 152.1075. Found: 152.1061.

*N*-[2-(3, 4-Dimethoxyphenyl)ethyl]dimethylamine<sup>[30]</sup> **3.46** (entry 6, Table 3.7)



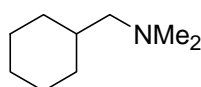
Following **general procedure XI**, using 3,4-dimethoxyphenethyl alcohol (0.18 g, 1 mmol), the title compound **3.46** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.11$  to give an oil (0.20 g, 94%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  6.82-6.74 (3H, m, ArH), 3.88 (3H, s, OCH<sub>3</sub>), 3.86 (3H, s, OCH<sub>3</sub>), 2.79-2.74 (2H, m, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.58-2.53 (2H, m, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.34 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  148.8 (C), 147.3 (C), 132.6 (C), 120.4 (CH), 111.8 (CH), 111.2 (CH), 61.6 (CH<sub>2</sub>), 55.9 (CH<sub>3</sub>), 55.8 (CH<sub>3</sub>), 45.4 (CH<sub>3</sub>), 33.8 (CH<sub>2</sub>). ESI-MS: Calculated for C<sub>12</sub>H<sub>20</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 210.1494. Found: 210.1473.

*N,N,N'*-Trimethyl-*N'*-phenyl-ethylenediamine<sup>[31]</sup> **3.48** (entry 7, Table 3.7)



Following **general procedure XI**, using 2-(methylphenylamino)ethanol (143  $\mu\text{L}$ , 1 mmol) at 2.5 mol% Ru, the title compound **3.48** was obtained and purified by column chromatography eluting with dichloromethane/methanol (95:5),  $R_f = 0.11$  to give an oil (0.13 g, 75%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.27-7.21 (2H, m, ArH), 6.74-6.67 (3H, m, ArH), 3.47 (2H, t,  $J = 7.6$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.96 (3H, s, CH<sub>3</sub>), 2.49 (2H, t,  $J = 7.6$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.31 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  149.1 (C), 129.2 (CH), 116.1 (CH), 112.0 (CH), 55.9 (CH<sub>2</sub>), 51.1 (CH<sub>2</sub>), 45.9 (CH<sub>3</sub>), 38.5 (CH<sub>3</sub>). ESI-MS: Calculated for C<sub>11</sub>H<sub>19</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 179.1548. Found: 179.1541.

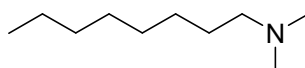
*N,N*-Dimethylcyclohexylmethylamine<sup>[32]</sup> **3.49** (entry 8, Table 3.7)



Following **general procedure XI**, using cyclohexylmethanol (0.123 mL, 1 mmol) at 2.5 mol% Ru, the title compound **3.49** was obtained and purified by column

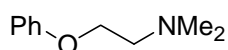
chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.1$  to give a brown oil (0.11 g, 77%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  2.28 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 2.17 (2H, app. t,  $J = 3.6$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 1.82-0.85 (11H, m, 5 $\text{CH}_2$ , 1  $\text{CH}$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  66.7 ( $\text{CH}_2$ ), 45.6 ( $\text{CH}_3$ ), 35.4 ( $\text{CH}$ ), 31.7 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_9\text{H}_{20}\text{N}$   $[\text{M}+\text{H}]^+$ : 142.1596. Found: 142.1589.

*N,N*-Dimethyloctylamine<sup>[33]</sup> **3.51** (entry 9, Table 3.12)



Following **general procedure XI**, using 1-octanol (0.157  $\mu\text{L}$ , 1 mmol) at 2.5 mol% Ru, the title compound **3.51** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.19$  to give a colourless oil (0.12 g, 76%).  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ (neat) 2929, 2856, 2763, 1466, 1379, 1261.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  2.27-2.19 (8H, m,  $\text{N}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 1.48-0.86 (15H, m, 6 $\text{CH}_2$ , 1  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  60.0 ( $\text{CH}_2$ ), 45.6 ( $\text{CH}_3$ ), 31.9 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 27.8 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 22.7 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{10}\text{H}_{24}\text{N}$   $[\text{M}+\text{H}]^+$ : 158.1903. Found: 158.1904.

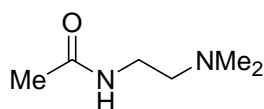
Dimethyl-(2-phenoxyethyl)amine<sup>[34]</sup> **3.53** (entry 10, Table 3.12)



Following **general procedure XI**, using ethylene glycol phenyl ether (0.125  $\mu\text{L}$ , 1 mmol) at 5 mol% Ru, the title compound **3.53** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.27$  to give a brown oil (0.13 g, 77%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  7.32-7.26 (2H, m,  $\text{ArH}$ ), 6.98-6.92 (3H, m,  $\text{ArH}$ ), 4.09 (2H, t,  $J = 5.7$  Hz,  $\text{OCH}_2$ ), 2.77 (2H, t,  $J = 5.7$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.37 (6H, s,  $\text{N}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  158.7 (C), 129.4 (CH), 120.8 (CH), 114.5 (CH), 65.7 ( $\text{CH}_2$ ), 58.3 ( $\text{CH}_2$ ), 45.8 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{10}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 166.1231. Found: 166.1226.

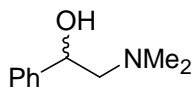


*N*-(2-Dimethylaminoethyl)acetamide<sup>[35]</sup> **3.55** (entry 10, Table 3.12)



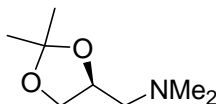
Following **general procedure XI**, using *N*-acetylaminoethanolamine (92  $\mu$ L, 1 mmol) at 5 mol% Ru, the title compound **3.55** was obtained and purified by column chromatography eluting with dichloromethane/methanol (80:20),  $R_f$  = 0.05 to give a pale yellow oil (94 mg, 72%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  3.32 (2H, app. q,  $J$  = 5.9 Hz,  $\text{NHCH}_2$ ), 2.42 (2H, t,  $J$  = 5.9 Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.24 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 1.98 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  170.2 (CO), 57.8 ( $\text{CH}_2$ ), 45.0 ( $\text{CH}_3$ ), 36.7 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_6\text{H}_{15}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 131.1184. Found: 131.1176.

( $\pm$ )-2-Dimethylamino-1-phenylethanol<sup>[36]</sup> **3.57** (Scheme 3.16)



Following **general procedure XI**, using (*R*)-(-)-1-phenyl-1,2-ethanediol (0.138 g, 1 mmol) at 1 mol% Ru, the title compound **3.57** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f$  = 0.06 to give a pale brown oil (0.13 g, 80%),  $[\alpha]_D^{25}$  0 ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  7.42-7.28 (5H, m Ph), 4.74 (1H, dd,  $J$  = 10.5, 3.5 Hz,  $\text{CHOH}$ ), 4.16 (1H, br. s, OH), 2.59-2.38 (2H, m,  $\text{CH}(\text{OH})\text{CH}_2$ ), 2.40 (6H, s,  $\text{N}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  142.1 (C), 128.3 (CH), 127.5 (CH), 125.8 (CH), 69.4 (CH), 67.4 ( $\text{CH}_2$ ), 45.2 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_{10}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 166.1232. Found: 166.1209.

(*S*)-[2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]dimethyl amine<sup>[37]</sup> **3.59** (Scheme 3.16)



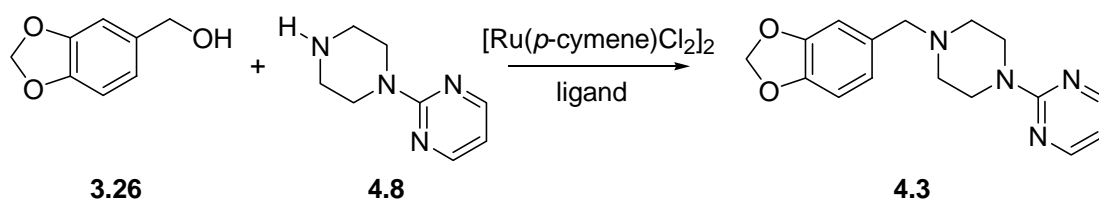
Following **general procedure XI**, using (*S*)-(+)-1,2-isopropylideneglycerol (0.124 mL, 1 mmol) at 1 mol% Ru, the title compound **3.59** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f$  = 0.16 to give an oil

(0.11 g, 70%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  4.24 (1H, m,  $\text{CHOC}(\text{CH}_3)_2$ ), 4.08 (1H, dd,  $J = 8.09$ , 6.20 Hz,  $\text{CHHOC}(\text{CH}_3)_2$ ), 3.59 (1H, dd,  $J = 8.04$ , 7.02 Hz,  $\text{CHHOC}(\text{CH}_3)_2$ ), 2.50 (1H, dd,  $J = 12.6$ , 7.0 Hz,  $\text{CHHN}(\text{CH}_3)_2$ ), 2.36 (1H, dd,  $J = 12.6$ , 5.2 Hz,  $\text{CHHN}(\text{CH}_3)_2$ ), 2.29 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 1.42 (3H, s,  $\text{CH}_3$ ), 1.36 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ):  $\delta$  109.2 (C), 73.9 (CH), 68.4 ( $\text{CH}_2$ ), 62.6 ( $\text{CH}_2$ ), 46.1 ( $\text{CH}_3$ ), 26.9 ( $\text{CH}_3$ ), 25.5 ( $\text{CH}_3$ ). ESI-MS: Calculated for  $\text{C}_8\text{H}_{18}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 160.1338. Found: 160.1329.

Enantiomeric resolution<sup>[4]</sup> (Appendix B) was achieved *via* 1:1 salt formation with (*S*)-(+)-O-acetylmandelic acid: (*S*)-[2,2-dimethyl-1,3-dioxolan-4-yl)methyl]dimethyl amine (0.009 g, 0.06 mmol) and (*S*)-(+)-O-acetylmandelic acid (0.011 g, 0.06 mmol) were dissolved in  $\text{CDCl}_3$  (0.6 mL). Analysis of the  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 25  $^\circ\text{C}$ ) spectrum and comparison with the racemic product revealed the splitting of the six proton dimethylamino peak and *ee* was calculated. Found: 28% *ee*.

## 5.4 Experimental Procedures for Chapter 4

### 5.4.1 General Procedure I for Screening of Catalyst and Ligand for Piribedil Synthesis as Summarised in Table 4.1



To an oven-dried, nitrogen purged carousel tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (7.7 mg, 0.0125 mmol), dppf (13.9 mg, 0.025 mmol), piperonyl alcohol (152.2 mg, 1 mmol) and activated molecular sieves (0.52 g, 3  $\text{\AA}$ ) was added 1-(2-pyrimidinyl)piperazine (142  $\mu\text{L}$ , 1 mmol) followed by anhydrous toluene (1 mL) dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. The solvent was then removed *in vacuo* and conversion was determined by analysis of the peak integral ratios characteristic of piribedil 4.3 and piperonyl aldehyde in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

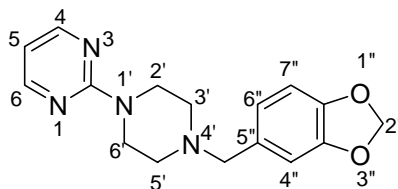
### Variation of dppf Loading

Following **general procedure I**, dppf loading was varied at 1 mol% (5.6 mg, 0.01 mmol) and 2.5 mol% (13.9 mg, 0.025 mmol) with 5 mol% of K<sub>2</sub>CO<sub>3</sub> (6.9 mg, 0.05 mmol) as described in Table 4.1, Section 4.3.2.

### Variation of DPEphos Loading

Following **general procedure I**, dppf was exchanged with DPEphos as the ligand and the ligand loading was varied at 1 mol% (5.4 mg, 0.01 mmol) and 2.5 mol% (13.5 mg, 0.025 mmol) with 5 mol% of K<sub>2</sub>CO<sub>3</sub> (6.9 mg, 0.05 mmol) as described in Table 4.1, Section 4.3.2.

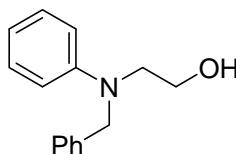
2-[4-(1,3-Benzodioxol-5-ylmethyl)-1-piperazinyl]pyrimidine **4.3** or Piribedil



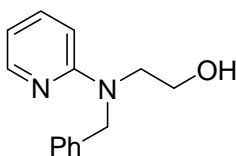
Following **general procedure I**, at 2.5 mol% Ru, the title compound **4.3** was obtained and purified by petroleum ether (b.p. 40-60 °C)/ethyl acetate (2:1), R<sub>f</sub> = 0.17 to give a pale yellow crystalline solid (0.25 g, 83%), m.p. 95-96 °C (Lit.<sup>[38]</sup> m.p. 95-98 °C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.3 (2H, d, *J* = 4.7 Hz, H<sub>4</sub>, H<sub>6</sub>), 6.90 (1H, s, H<sub>4''</sub>), 6.78<sup>[a]</sup> (1H, d, *J* = 8.2 Hz, H<sub>7''</sub>), 6.76<sup>[a]</sup> (1H, d, *J* = 6.9 Hz, H<sub>6''</sub>) (<sup>[a]</sup> these signals appear as a very strongly roofed AB system), 6.47 (1H, t, *J* = 4.7 Hz, H<sub>5</sub>), 5.96 (2H, s, H<sub>2''</sub>), 3.83 (4H, t, *J* = 5.1 Hz, H<sub>2'</sub>, H<sub>6'</sub>), 3.46 (2H, s, ArCH<sub>2</sub>), 2.49 (4H, t, *J* = 5.1 Hz, H<sub>3'</sub>, H<sub>5'</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C): δ 161.7 (C), 157.7 (CH), 147.7 (C), 146.7 (C), 131.9 (C), 122.2 (CH), 109.7 (CH), 109.5 (CH), 107.9 (CH), 100.9 (CH<sub>2</sub>), 62.9 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>), 43.7 (CH<sub>2</sub>). ESI-MS: Calculated for C<sub>16</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 299.1508. Found: 299.1506.

### 5.4.2 Synthesis of 2-(*N*-Benzyl-*N*-phenylamino)ethanol and 2-(*N*-Benzyl-pyridin-2-yl-amino)ethanol via Conventional Alkylation Reaction (Scheme 4.6)

2-(*N*-Benzyl-*N*-phenylamino)ethanol<sup>[39]</sup> **4.20**

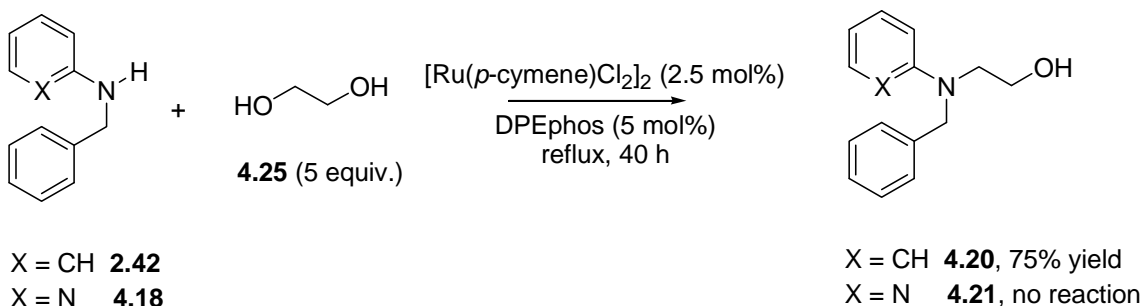


To a two-necked round bottom flask was added 2-bromoethanol (0.77 mL, 0.011 mol), acetonitrile (2.5 mL) and potassium iodide (1.82 g, 0.011 mol) and left to stir for 5 minutes to form a yellow solution.<sup>[40]</sup> In another two-necked round bottom flask was added *N*-benzylaniline (2.00 g, 0.011 mol), acetonitrile (5 mL) and NaHCO<sub>3</sub> (0.92 g) and left to stir for 5 minutes and the 2-bromoethanol mixture was added to it. The mixture was heated to reflux for 17 hours. An NMR sample was taken which showed unreacted starting material. Therefore, another portion of bromoethanol /MeCN/KI mixture was added and reflux was continued for another 17 hours. After being allowed to cool, the solvent was then removed *in vacuo* and HCl (1.5 M, 80 mL) was added to the crude mixture and then extracted two times with CH<sub>2</sub>Cl<sub>2</sub> (90 mL). In order to isolate the aminoalcohol, the combined aqueous HCl layers were neutralised with NaOH (1.5 M, 90 mL, pH = 14) and then extracted two times with CH<sub>2</sub>Cl<sub>2</sub> (90 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous MgSO<sub>4</sub> and the solvent was removed *in vacuo* to give the title compound **4.20** as a colourless oil (1.01 g, 40%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C): δ 7.34-7.18 (7H, m, ArH), 6.81-6.71 (3H, m, ArH), 4.63 (2H, s, PhCH<sub>2</sub>), 3.84 (2H, app. q, *J* = 5.8 Hz, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.62 (2H, t, *J* = 5.8 Hz, NCH<sub>2</sub>CH<sub>2</sub>OH); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C): δ 148.8 (C), 138.6 (C), 129.3 (CH), 128.6 (CH), 126.9 (CH), 126.6 (CH), 117.1 (CH), 113.0 (CH), 60.3 (CH<sub>2</sub>), 55.1 (CH<sub>2</sub>), 53.4 (CH<sub>2</sub>). ESI-MS: Calculated for C<sub>15</sub>H<sub>18</sub>NO [M+H]<sup>+</sup>: 228.1388. Found: 228.1385.

2-(*N*-benzyl-pyridin-2-yl-amino)ethanol **4.21**

To a two-necked round bottom flask was added 2-bromopyridine (1.2 mL, 0.0126 mol) and 2-benzylaminoethanol (3.6 mL, 0.025 mol). The mixture was heated to reflux at 173 °C in a silicon oil-bath for 19 hours.<sup>[41]</sup> After being allowed to cool, the mixture was dissolved in chloroform (10 mL) and transferred to a separating funnel. The chloroform solution was shaken with 20 mL of saturated potassium carbonate solution to neutralise the hydrogen bromide formed in the reaction. The chloroform solution was dried over potassium carbonate and the solvent removed *in vacuo*. The residue was purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/diethyl ether (1:1),  $R_f = 0.09$  to give the title compound **4.21** as a pale-brown oil (0.84 g, 29%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  8.10-8.08 (1H, m, py), 7.42-7.21 (6H, m, py, Ph), 6.60 (1H, dd,  $J = 7.1$  Hz, 5.1 Hz, py), 6.47 (1H, d,  $J = 8.7$  Hz, py), 4.67 (2H, s,  $\text{PhCH}_2$ ), 3.89-3.80 (4H, m,  $\text{NCH}_2\text{CH}_2\text{OH}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  159.1 (C), 146.9 (CH), 137.9 (CH), 137.5 (C), 128.8 (CH), 127.1 (CH), 126.3 (CH), 112.7 (CH), 107.0 (CH), 63.3 ( $\text{CH}_2$ ), 53.7 ( $\text{CH}_2$ ), 52.9 ( $\text{CH}_2$ ). ESI-MS: Calculated for  $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 229.1341. Found: 229.1337.

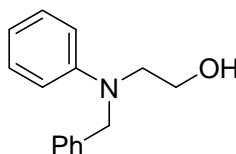
### 5.4.3 General Procedure II for the Synthesis of 2-(*N*-Benzyl-*N*-phenylamino)ethanol and 2-(*N*-Benzyl-pyridin-2-yl-amino)ethanol *via* Borrowing Hydrogen (Scheme 4.7)



To an oven-dried, nitrogen-purged Schlenk tube containing  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  (15.3 mg, 0.025 mmol) and DPEphos (26.9 mg, 0.05 mmol) was added the respective benzylamine followed by ethylene glycol (279  $\mu\text{L}$ , 5 mmol). Anhydrous toluene (1 mL) was then added dropwise. The reaction mixture was stirred under a nitrogen

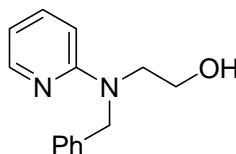
atmosphere at room temperature for 10 minutes and then heated to reflux for three days. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo*.

2-(*N*-Benzyl-*N*-phenylamino)ethanol<sup>[39]</sup> **4.20**



Following **general procedure II**, *N*-benzylaniline (0.18 g, 1 mmol) was used in the reaction. The title compound **4.20** was obtained and purified by column chromatography eluting with petroleum ether/diethyl ether (1:1),  $R_f = 0.29$  to give a colourless oil (0.16 g, 70%). The spectroscopy data was consistent with the analytical data reported previously (Section 5.4.2).

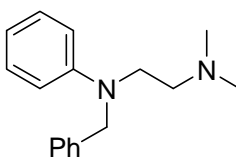
Attempted Synthesis of 2-(*N*-Benzyl-pyridin-2-yl-amino)ethanol **4.21**



Following **general procedure II**, *N*-benzylamino pyridine (0.18 g, 1 mmol) was used in the reaction but recovered starting material was only obtained after the reaction.

#### 5.4.4 Ruthenium-Catalysed Synthesis of Antergan and Tripelennamine (Scheme 4.8)

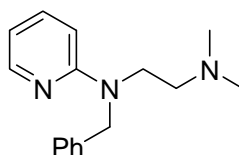
*N*-Benzyl-*N*',*N*'-dimethyl-*N*-phenyl-ethylenediamine **1.5** or Antergan<sup>[42]</sup>



Following **general procedure XI** (Section 5.3.16), using *N*-benzyl-2-anilinoethanol (0.23 g, 1 mmol) at 5 mol% Ru, the title compound **1.5** was obtained and purified by

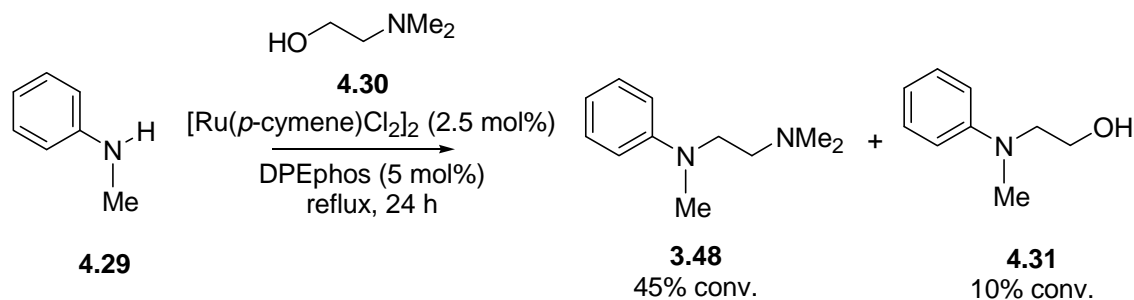
column chromatography eluting with dichloromethane/methanol (95:5),  $R_f = 0.28$  to give an oil (0.19 g, 75%).  $\nu_{\max}$  /cm<sup>-1</sup>(neat) 3027, 2943, 2768, 1598, 1506, 1452, 1356. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  7.34-7.17 (7H, m, ArH), 6.73-6.67 (3H, m, ArH), 4.58 (2H, s, PhCH<sub>2</sub>), 3.58 (2H, t,  $J = 7.6$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.59 (2H, t,  $J = 7.6$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.32 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  148.3 (C), 138.8 (C), 129.3 (CH), 128.6 (CH), 126.8 (CH), 126.6 (CH), 116.4 (CH), 112.2 (CH), 56.2 (CH<sub>2</sub>), 54.8 (CH<sub>2</sub>), 49.3 (CH<sub>2</sub>), 45.7 (CH<sub>3</sub>). ESI-MS: Calculated for C<sub>17</sub>H<sub>23</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 255.1861. Found: 255.1862.

*N*-Pyridyl-*N,N'*-dimethyl-*N*-phenyl-ethylenediamine **1.6** or Tripeleennamine<sup>[43]</sup>



Following **general procedure XI** (Section 5.3.16), using *N*-benzyl-2-aminopyridylethanol (0.23 g, 1 mmol) at 5 mol% Ru, the title compound **1.6** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1),  $R_f = 0.17$  to give pale yellow liquid (0.19 g, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.17-8.15 (1H, m, py), 7.40 (1H, , dd,  $J = 8.6$  Hz, 7.1 Hz, py), 7.34-7.22 (5H, m, ArH), 6.57 (1H, dd,  $J = 7.1$  Hz, 5.0 Hz, py), 6.48 (1H, d,  $J = 8.6$  Hz, py), 4.77 (2H, s, PhCH<sub>2</sub>), 3.79 (2H, t,  $J = 7.3$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.70 (2H, t,  $J = 7.1$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.41 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  158.0 (C), 148.0 (CH), 138.5 (C), 137.3 (CH), 128.6 (CH), 127.0 (CH), 126.8 (CH), 112.1 (CH), 106.0 (CH), 56.3 (CH<sub>2</sub>), 52.2 (CH<sub>2</sub>), 46.0 (CH<sub>2</sub>), 45.2 (CH<sub>3</sub>). ESI-MS: Calculated for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 256.1814. Found: 256.1806.

### 5.4.5 General Procedure III for the Alkylation of *N*-Methylaniline by Borrowing Hydrogen



To an oven-dried, nitrogen-purged Schlenk tube containing  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (7.7 mg, 0.0125 mmol) and DPEphos (13.5 mg, 0.025 mmol) was added *N*-methylaniline (108  $\mu\text{L}$ , 1 mmol) followed by *N,N*-dimethylaminoethanol (101  $\mu\text{L}$ , 1 mmol). Anhydrous toluene (1 mL) was then added dropwise. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo*. Conversion was determined by analysis of the peak integral ratios characteristic of amine product **3.48** and alcohol **4.31** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

#### Attempted Alkylation of *N*-Methylaniline with TMEDA

Following **general procedure III**, *N,N*-dimethylaminoethanol was exchanged with TMEDA (150  $\mu\text{L}$ , 1 mmol) was used in the reaction.

#### Alkylation of *N*-Methylaniline with *N,N*-Dimethylaminopropanol

Following **general procedure III**, *N,N*-dimethylaminoethanol was exchanged with *N,N*-dimethylaminopropanol (118  $\mu\text{L}$ , 1 mmol) was used in the reaction.

## 5.5 References

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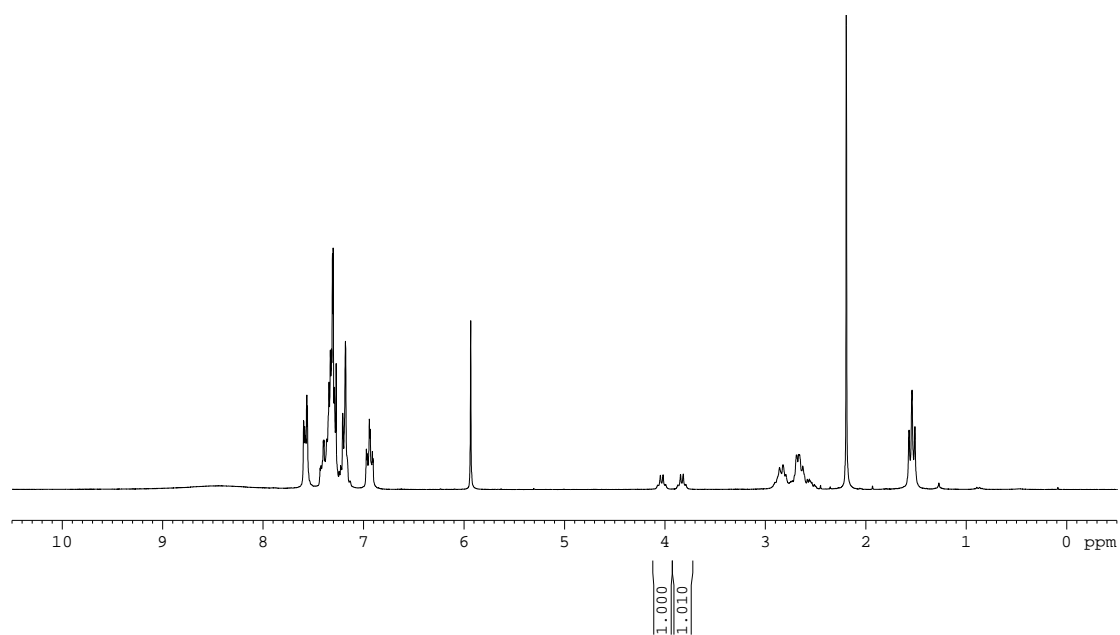


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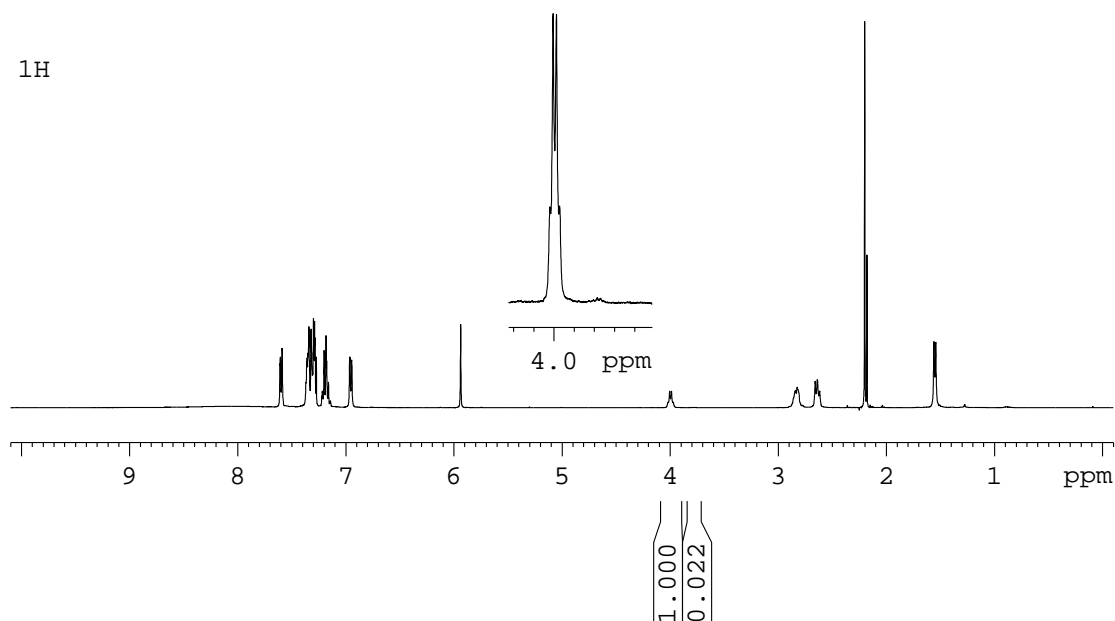
## Appendix A

(±)-Phenethyl-(1-phenylethyl)amine + (*S*)-(+)-O-Acetyl Mandelic Acid

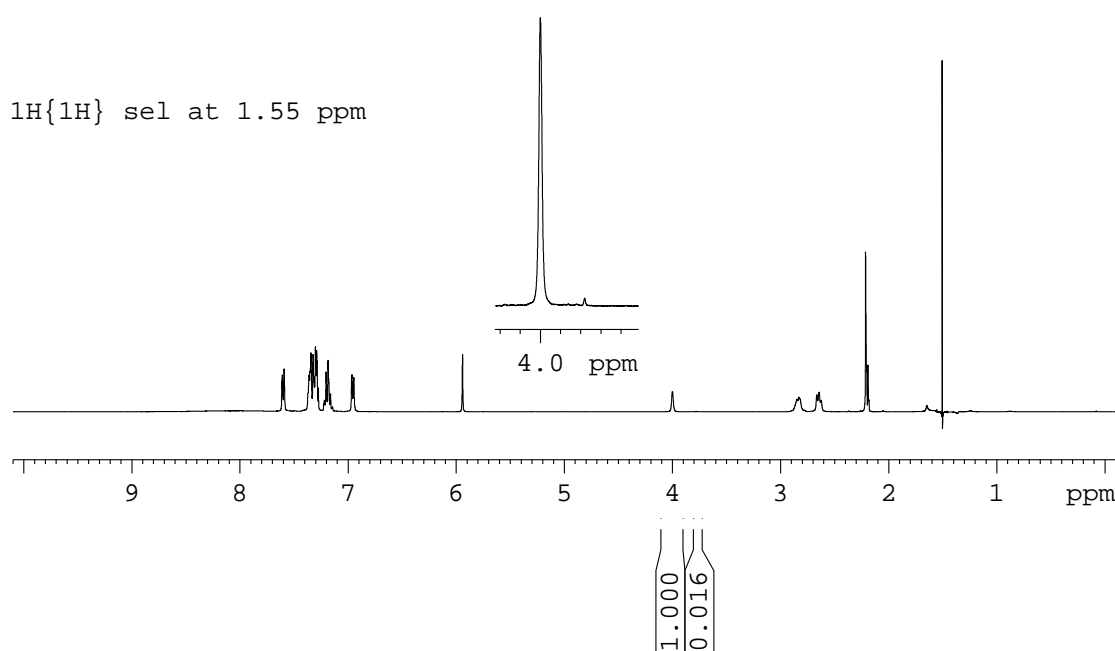


(*R*)- $\alpha$ -Phenethyl-(1-phenylethyl)amine + (*S*)-(+)-O-Acetyl Mandelic Acid

(a)



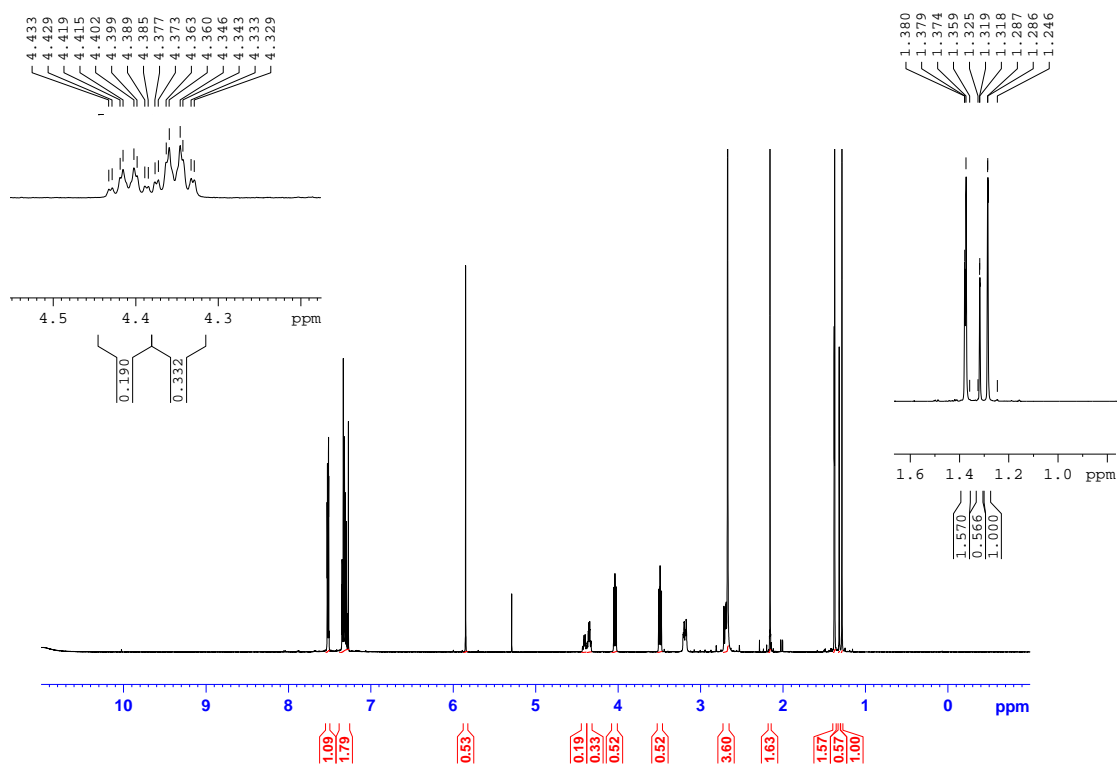
(b)



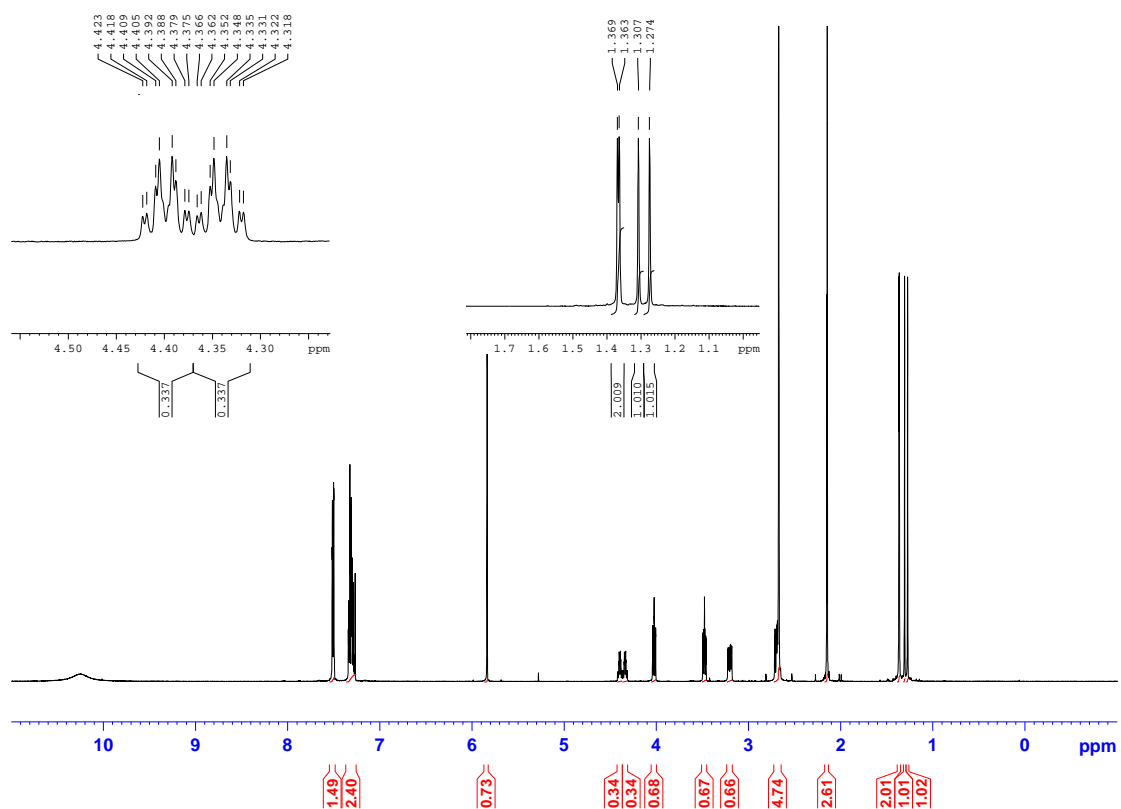
Spectrum (a) shows a quartet at  $\delta$  4.00 that has been decoupled allowing a rough integration of 1.000:0.022 for the enantiomers. The original spectrum was difficult to resolve and therefore we irradiated at  $\delta$  1.55 to give 2 singlets at an integration of 1.000:1.016 shown in spectrum (b) from which the ee was calculated and found to be 97% ee.

## Appendix B

(*S*)-[2,2-dimethyl-1,3-dioxolan-4-yl)methyl]dimethyl amine **3.58** + (*S*)-(+)-O-Acetylmandelic Acid

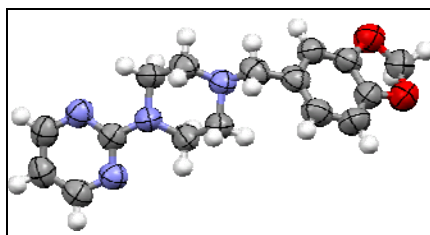


(±)-[2,2-dimethyl-1,3-dioxolan-4-yl)methyl]dimethyl amine + (S)-(+)-O-Acetyl  
Mandelic Acid



## Appendix C

Piribedil {2-[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]pyrimidine, Trivastal<sup>®</sup>} **4.3**



**Table 1.** Crystal data and structure refinement for **4.3**.

Identification code	k07jmw1
Empirical formula	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>
Formula weight	298.34
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pnaa
Unit cell dimensions	a = 7.4020(1) Å $\angle = 90^\circ$
	b = 18.4680(3) Å $\angle = 90^\circ$
	c = 21.2280(4) Å $\angle = 90^\circ$
Volume	2901.87(8) Å <sup>3</sup>
Z	8
Density (calculated)	1.366 Mg/m <sup>3</sup>
Absorption coefficient	0.093 mm <sup>-1</sup>
F(000)	1264
Crystal size	0.30 x 0.30 x 0.15 mm
Theta range for data collection	3.53 to 27.49 °
Index ranges	-8 ≤ h ≤ 9; -23 ≤ k ≤ 23; -27 ≤ l ≤ 27
Reflections collected	52865
Independent reflections	3325 [R(int) = 0.0784]
Reflections observed (>2σ)	2545
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.90
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3325 / 0 / 199
Goodness-of-fit on F <sup>2</sup>	1.095
Final R indices [I > 2σ(I)]	R <sup>1</sup> = 0.0442 wR <sub>2</sub> = 0.0909
R indices (all data)	R <sup>1</sup> = 0.0669 wR <sub>2</sub> = 0.1009
Largest diff. peak and hole	0.176 and -0.213 eÅ <sup>-3</sup>

**Table 2.** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 1. U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

Atom	x	y	z	U(eq)
O(1)	9522(2)	-2751(1)	486(1)	33(1)
O(2)	10412(2)	-3019(1)	1503(1)	37(1)
N(1)	7020(2)	26(1)	922(1)	24(1)
N(2)	3884(2)	845(1)	1243(1)	26(1)
N(3)	1704(2)	1682(1)	944(1)	27(1)
N(4)	1705(2)	1153(1)	1979(1)	26(1)
C(1)	9637(2)	-3322(1)	942(1)	33(1)
C(2)	9595(2)	-2123(1)	837(1)	26(1)
C(3)	9250(2)	-1429(1)	644(1)	27(1)
C(4)	9464(2)	-873(1)	1092(1)	26(1)
C(5)	10056(2)	-1040(1)	1694(1)	32(1)
C(6)	10414(2)	-1751(1)	1885(1)	36(1)
C(7)	10144(2)	-2283(1)	1445(1)	30(1)
C(8)	8987(2)	-106(1)	913(1)	29(1)
C(9)	6605(2)	715(1)	614(1)	27(1)
C(10)	4593(2)	853(1)	600(1)	27(1)
C(11)	4340(2)	189(1)	1594(1)	28(1)
C(12)	6355(2)	52(1)	1573(1)	27(1)
C(13)	2365(2)	1235(1)	1391(1)	23(1)
C(14)	272(2)	2079(1)	1114(1)	29(1)
C(15)	-494(2)	2045(1)	1704(1)	30(1)
C(16)	289(2)	1566(1)	2123(1)	29(1)



**Table 3.** Bond lengths [Å] and angles [°] for **4.3**.

O(1)-C(2)	1.3795(17)
O(1)-C(1)	1.4340(18)
O(2)-C(7)	1.3804(18)
O(2)-C(1)	1.4351(19)
N(1)-C(9)	1.4639(18)
N(1)-C(12)	1.4677(18)
N(1)-C(8)	1.4764(19)
N(2)-C(13)	1.3720(18)
N(2)-C(10)	1.4612(18)
N(2)-C(11)	1.4625(18)
N(3)-C(14)	1.3379(19)
N(3)-C(13)	1.3487(18)
N(4)-C(16)	1.3320(19)
N(4)-C(13)	1.3484(18)
C(2)-C(3)	1.370(2)
C(2)-C(7)	1.385(2)
C(3)-C(4)	1.409(2)
C(4)-C(5)	1.387(2)
C(4)-C(8)	1.507(2)
C(5)-C(6)	1.400(2)
C(6)-C(7)	1.370(2)
C(9)-C(10)	1.512(2)
C(11)-C(12)	1.514(2)
C(14)-C(15)	1.376(2)
C(15)-C(16)	1.382(2)
C(2)-O(1)-C(1)	104.55(11)
C(7)-O(2)-C(1)	104.64(11)
C(9)-N(1)-C(12)	108.80(11)
C(9)-N(1)-C(8)	110.20(11)
C(12)-N(1)-C(8)	110.28(11)
C(13)-N(2)-C(10)	120.20(12)
C(13)-N(2)-C(11)	120.50(12)
C(10)-N(2)-C(11)	113.65(11)
C(14)-N(3)-C(13)	115.67(13)
C(16)-N(4)-C(13)	115.66(13)
O(1)-C(1)-O(2)	107.29(12)
C(3)-C(2)-O(1)	128.10(13)
C(3)-C(2)-C(7)	122.23(13)
O(1)-C(2)-C(7)	109.65(13)
C(2)-C(3)-C(4)	117.33(13)
C(5)-C(4)-C(3)	119.68(14)
C(5)-C(4)-C(8)	120.96(13)
C(3)-C(4)-C(8)	119.33(13)
C(4)-C(5)-C(6)	122.44(14)
C(7)-C(6)-C(5)	116.55(14)
C(6)-C(7)-O(2)	128.66(14)
C(6)-C(7)-C(2)	121.73(14)

O(2)-C(7)-C(2)	109.56(13)
N(1)-C(8)-C(4)	112.56(12)
N(1)-C(9)-C(10)	111.18(12)
N(2)-C(10)-C(9)	109.56(12)
N(2)-C(11)-C(12)	110.56(12)
N(1)-C(12)-C(11)	111.32(12)
N(4)-C(13)-N(3)	126.02(13)
N(4)-C(13)-N(2)	116.74(12)
N(3)-C(13)-N(2)	117.21(13)
N(3)-C(14)-C(15)	123.13(14)
C(14)-C(15)-C(16)	116.26(14)
N(4)-C(16)-C(15)	123.26(14)

Symmetry transformations used to generate equivalent atoms:

**Table 4.** Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for **4.3**. The anisotropic displacement factor exponent takes the form:  $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

Atom	U11	U22	U33	U23	U13	U12
O(1)	44(1)	29(1)	27(1)	-1(1)	-2(1)	3(1)
O(2)	47(1)	33(1)	29(1)	3(1)	0(1)	9(1)
N(1)	24(1)	25(1)	23(1)	0(1)	4(1)	1(1)
N(2)	30(1)	26(1)	21(1)	3(1)	4(1)	4(1)
N(3)	28(1)	27(1)	26(1)	0(1)	-4(1)	1(1)
N(4)	25(1)	29(1)	25(1)	0(1)	2(1)	0(1)
C(1)	37(1)	30(1)	31(1)	2(1)	2(1)	4(1)
C(2)	25(1)	31(1)	23(1)	-4(1)	2(1)	2(1)
C(3)	25(1)	33(1)	22(1)	1(1)	0(1)	2(1)
C(4)	21(1)	32(1)	27(1)	-1(1)	4(1)	0(1)
C(5)	33(1)	37(1)	26(1)	-7(1)	0(1)	3(1)
C(6)	40(1)	44(1)	23(1)	0(1)	-3(1)	7(1)
C(7)	29(1)	33(1)	27(1)	3(1)	3(1)	6(1)
C(8)	26(1)	30(1)	30(1)	-1(1)	5(1)	-2(1)
C(9)	32(1)	25(1)	25(1)	0(1)	5(1)	-2(1)
C(10)	32(1)	27(1)	21(1)	0(1)	3(1)	3(1)
C(11)	31(1)	26(1)	28(1)	5(1)	6(1)	4(1)
C(12)	30(1)	28(1)	23(1)	2(1)	3(1)	3(1)
C(13)	24(1)	21(1)	24(1)	-2(1)	-2(1)	-3(1)
C(14)	29(1)	27(1)	32(1)	1(1)	-6(1)	2(1)
C(15)	26(1)	30(1)	35(1)	-2(1)	-1(1)	4(1)
C(16)	26(1)	31(1)	29(1)	-2(1)	4(1)	0(1)

**Table 5.** Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for **4.3**.

Atom	x	y	z	U(eq)
H(1A)	10405	-3720	781	39
H(1B)	8420	-3519	1032	39
H(3)	8880	-1327	224	32
H(5)	10225	-658	1988	39
H(6)	10823	-1859	2299	43
H(8A)	9581	231	1211	34
H(8B)	9459	-3	487	34
H(9A)	7077	708	177	32
H(9B)	7213	1114	842	32
H(10A)	4347	1329	403	32
H(10B)	3986	475	346	32
H(11A)	3693	-230	1410	34
H(11B)	3947	242	2037	34
H(12A)	6990	441	1804	32
H(12B)	6626	-414	1784	32
H(14)	-239	2400	813	35
H(15)	-1505	2334	1816	36
H(16)	-206	1530	2535	34